7. PASSIVE SMOKING AND RESPIRATORY DISORDERS OTHER THAN CANCER

7.1. INTRODUCTION

In 1984, a report of the Surgeon General identified cigarette smoking as the major cause of chronic obstructive lung disease in the United States (U.S. DHHS, 1984). The same report stated that there is conclusive evidence showing that smokers are at increased risk of developing respiratory symptoms such as chronic cough, chronic phlegm production, and wheezing (U.S. DHHS, 1984). More recently, longitudinal studies have demonstrated accelerated decline in lung function in smoking adults (Camilli et al., 1987). In children and adolescents who have recently taken up smoking, several cross-sectional studies have found statistically significant increases in the prevalence of respiratory symptoms (cough, phlegm production, and dyspnea [i.e., shortness of breath]) (Seely et al., 1971; Bewley et al., 1973). Longitudinal studies also have demonstrated that, among young teenagers, functional impairment attributable to smoking may be found after as little as 1 year of smoking 10 or more cigarettes per week (Woolcock et al., 1984).

From a pathophysiologic point of view, smoking is associated with significant structural changes in both the airways and the pulmonary parenchyma (U.S. DHHS, 1984). These changes include hypertrophy and hyperplasia of the upper airway mucus glands, leading to an increase in mucus production, with an accompanying increased prevalence of cough and phlegm. Chronic inflammation of the smaller airways leads to bronchial obstruction. However, airway narrowing also may be due to the destruction of the alveolar walls and the consequent decrease in lung elasticity and development of centrilobular emphysema (Bellofiore et al., 1989). Smoking also may increase mucosal permeability to allergens. This may result in increased total and specific IgE levels (Zetterstrom et al., 1981) and increased blood eosinophil counts (Halonen et al., 1982).

The ascertained consequences of active smoking on respiratory health, and the fact that significant effects have been observed at relatively low-dose exposures, lead to an examination for similar effects with environmental tobacco smoke (ETS). Unlike active smoking, involuntary exposure to ETS (or "passive smoking") affects individuals of all ages, particularly infants and children. An extensive analysis of respiratory effects of ETS in children suggests that the lung of the young child may be particularly susceptible to environmental insults (NRC, 1986). Exposures in early periods of life during which the lung is undergoing significant growth and remodeling may alter the pattern of lung development and increase the risk for both acute and chronic respiratory illnesses.

Acute respiratory illnesses are one of the leading causes of morbidity and mortality during infancy and childhood. One-third of all infants have at least one lower respiratory tract illness (bronchitis, bronchiolitis, croup, or pneumonia) during the first year of life (Wright et al., 1989), whereas approximately one-fourth have these same illnesses during the second and third years of life (Gwinn et al., 1991). The high incidence of these potentially severe illnesses has an important consequence from a public health viewpoint: Even small increases in risk due to passive exposure to ETS would considerably increase the absolute number of cases in the first 3 years of life (see Chapter 8). In addition, several studies have shown that lower respiratory tract illnesses occurring early in life are associated with

a significantly higher prevalence of asthma and other chronic respiratory diseases and with lower levels of respiratory function later in life (reviewed extensively by Samet and collaborators [1983]).

This chapter reviews and analyzes epidemiologic studies of noncancer respiratory system effects of passive smoking, starting with possible biological mechanisms (Section 7.2). The evidence indicating a relationship between exposure to ETS during childhood and acute respiratory illnesses (Section 7.3), middle ear diseases (Section 7.4), chronic respiratory symptoms (Section 7.5), asthma (Section 7.6), sudden infant death syndrome (Section 7.7), and lung function impairment (Section 7.8) is evaluated. Passive smoking as a risk factor for noncancer respiratory illnesses and lower lung function in adults also is analyzed (Section 7.9). A health hazard assessment and population impact is presented in the next chapter.

7.2. BIOLOGICAL MECHANISMS

7.2.1. Plausibility

It is plausible that passive smoking may produce effects similar to those known to be elicited by active smoking. However, several differences both between active and passive forms of exposure and among the individuals exposed to them need to be considered.

The concentration of smoke components inhaled by subjects exposed to ETS is small compared with that from active smoking. Therefore, effect will be highly dependent on the nature of the dose-response curve (NRC, 1986). It is likely that there is a distribution of susceptibility to the effects of ETS that may depend on, among other factors, age, gender, genetic predisposition, respiratory history, and concomitant exposure to other risk factors for the particular outcome being studied. The ability to ascertain responses to very low concentrations also depends on the reliability and sensitivity of the instruments utilized.

Breathing patterns for the inhalation of mainstream smoke (MS) and ETS differ considerably; active smokers inhale intensely and intermittently and usually hold their breath for some time at the end of inspiration. This increases the amount of smoke components that are deposited and absorbed (U.S. DHHS, 1986). Passive smokers inhale with tidal breaths and continuously. Therefore, patterns of particle deposition and gas diffusion and absorption differ considerably for these two types of inhalation.

There are also important differences in the physicochemical properties of ETS and MS (see Chapter 3). These have been extensively reviewed earlier by the National Research Council (NRC, 1986) and the Surgeon General (U.S. DHHS, 1986). ETS is a combination of exhaled MS, sidestream smoke (that is, the aerosol that is emitted from the burning cone between puffs), smoke emitted from the burning side of the cigarette during puffs, and gases that diffuse through the cigarette paper into the environment. This mixture may be modified by reactions that occur in the air before involuntary inhalation. This "aging" process includes volatilization of nicotine, which is present in the particulate phase in MS but is almost exclusively a component of the vapor phase of ETS. Aging of

ETS also entails a decrease in the mean diameter of its particles from 0.32 μm to 0.1-0.14 μm, compared to a mean particle diameter for MS of 0.4 μm (NRC, 1986).

Individual and socioeconomic susceptibility may be important determinants of possible effects of ETS on respiratory health. A self-selection process almost certainly occurs among subjects who experiment with cigarettes, whereby those more susceptible to the irritant or sensitizing effects of tobacco smoke either never start or quit smoking (the so-called "healthy smoker" effect). Infants, children, and nonsmoking adults thus may include a disproportionate number of susceptible subjects when compared with smoking adults. In addition, recent studies clearly have shown that, as incidence and prevalence of cigarette smoking has decreased, the socioeconomic characteristics of smokers also have changed. Among smokers, the proportion of subjects of lower educational level has increased in the past 20 years (Pierce et al., 1989). The female-to-male ratio also has increased (Fiore et al., 1989), and this is particularly true for young, poor women, in whom incidence and prevalence of smoking has increased (Williamson et al., 1989). It is thus possible that exposure to ETS may be most prevalent today among precisely those infants and children who are known to be at a high risk of developing respiratory illnesses early in life.

7.2.2. Effects of Exposure In Utero and During the First Months of Life

A factor that may significantly modify the effect of passive smoking (particularly in children) is exposure to tobacco smoke components by the fetus during pregnancy. This type of exposure differs considerably from passive smoking; in fact, the fetus (including its lungs) is exposed to components of tobacco smoke that are absorbed by the mother and that cross the placental barrier, whereas passive smoking directly affects the bronchial mucosa and the alveolus. It is difficult to distinguish between the possible effects of smoking during pregnancy and those of ETS exposure after birth. Some women may quit smoking during pregnancy, only to resume after pregnancy is over. Most mothers who smoke during pregnancy continue smoking after the birth of their child (Wright et al., 1991), and among those who stop smoking after birth, the influence on that decision of events occurring shortly after birth (such as respiratory illnesses in their child) cannot be excluded. Recall bias also may influence the results of retrospective studies claiming differential effects on lung function of prenatal and postnatal maternal smoking habits (Yarnell and St. Leger, 1979).

To attempt to circumvent these problems, researchers have studied infant lung function shortly after birth (the youngest group of infants reported was 2 weeks old [Neddenriep et al., 1990]), with the implication that subsequent changes encountered could be attributed mainly to ETS exposure. However, the possibility that even brief exposure to ETS may affect the lungs at a highly susceptible age may not be discarded. Maternal smoking during pregnancy needs to be considered, therefore, as a potential modifier of the effect of passive smoking on respiratory health, particularly in children.

Exposure to compounds present in tobacco smoke may affect the fetal and neonatal lung and alter lung structure much like these same compounds do in smoking adults. Neddenriep and coworkers (1990) studied 31 newborns and reported that those whose mothers smoked during pregnancy had significant increases in specific lung

compliance (i.e., lung compliance/lung volume) at 2 weeks of age when compared with infants of nonsmoking mothers. The authors concluded that exposure to tobacco products detrimentally affects the elastic properties of the fetal lung. Although these effects also could be attributed to postnatal exposure to ETS, it is unlikely that such a brief period of postnatal exposure would be responsible for these changes affecting the lung parenchyma (U.S. DHHS, 1986).

There is evidence for similar effects of prenatal lung development in animal models. Collins and associates (1985) exposed pregnant rats to MS during day 5 to day 20 of gestation. They found that pups of exposed rats showed reduced lung volume, reduced number of lung saccules, and reduced length of elastin fibers in the lung interstitium. This apparently resulted in a decrease in lung elasticity: For the same inflation pressure, pups of exposed mothers had significantly higher weight-corrected lung volumes than did pups of unexposed mothers. Vidic and coworkers (1989) exposed female rats for 6 months (including mating and gestation) to MS. They found that lungs of their 15-day-old pups had less parenchymal tissue, less extracellular matrix, less collagen, and less elastin than found in lungs of control animals. This may explain the increased lung compliance observed by Collins et al. (1985) in pups exposed to tobacco smoke products in utero.

Hanrahan and coworkers (1990) reported that infants born to smoking mothers had significantly reduced levels of forced expiratory flows. The researchers studied 80 mother/child pairs and found significant correlations between the cotinine/creatinine ratio in urine specimens obtained during pregnancy in the mother and maximal expiratory flows and tidal volumes at a postconceptional age of 50 weeks or younger in their children. The investigators concluded that exposure due to prenatal smoking diminishes infant pulmonary function at birth and, by inference, airway size. These authors also measured maximal flows during tidal breathing in their subjects. At rather low lung volumes, such as those present during tidal breathing, airway size and maximal flows are both a function of lung elasticity. These results thus may be due to both a specific alteration of the infant's airways and an increased lung compliance in infants whose lungs are small relative to the infant's length.

It also has been suggested that the increased IgE levels observed in adult smokers also may be present in fetuses whose mothers smoke during pregnancy. Magnusson (1986) reported that cord serum levels of IgE and IgD were significantly higher for neonates whose mothers smoked during pregnancy, particularly if the neonates had no parental history of allergic disorders. Cord serum levels of IgD (but not of IgE) were increased for neonates whose fathers smoked, and this effect was independent of maternal smoking. A more recent study on a larger sample (more than 1,000 neonates) failed to find any significant difference in cord serum IgE levels between infants (N = 193) of mothers who smoked during pregnancy and those (N = 881) of mothers who did not (Halonen et al., 1991).

It also has been reported recently that the pulmonary neuroendocrine system may be altered in infants whose mothers smoke during pregnancy. The pulmonary neuroendocrine system, located in the tracheobronchial tree, consists of specialized cells (isolated or in clusters called "neuroepithelial bodies") that are closely related to nerves. In humans, these cells increase in number significantly during intrauterine development, reach a maximum around birth, and then rapidly decline during the first 2 years of life. Their function is not well understood, but the presence

of potent growth factors and bronchoconstrictive substances in their granules suggests that they play an important role in growth regulation and airway tone control during this period of lung development (Stahlman and Gray, 1984). Chen and coworkers (1987) reported that maternal smoking during pregnancy increases the size of infant lung neuroepithelial bodies and decreases the amount of core granules present in them. Wang and coworkers (1984) had reported previously that mother mice receiving tap water with nicotine during pregnancy and during lactation had offspring with increased numbers of neuroepithelial bodies at 5 days of age when compared with baby mice whose mothers were not exposed. Baby mice exposed to nicotine only during pregnancy had neuroepithelial bodies of intermediate size with respect to these two groups, whereas those exposed only during lactation had neuroepithelial bodies of normal size. By age 30 days, only baby mice exposed to nicotine during both pregnancy and lactation had neuroepithelial bodies that were larger than those of control animals.

Activation of the pulmonary neuroendocrine system is not limited to ETS exposure; it is activated by active smoking as well. Aguayo and collaborators (1989) reported that bronchoalveolar lavage fluids obtained from healthy smokers have increased levels of bombesin-like peptides, which are a normal component and a secretion product of human lung neuroendocrine cells (Cutz et al., 1981).

In summary, effects of maternal smoking during pregnancy on the fetus are difficult to distinguish from those elicited by early postnatal exposure to ETS. Animal studies suggest that postnatal exposure to tobacco products enhances the effects of in utero exposure to these same products.

7.2.3. Long-Term Significance of Early Effects on Airway Function

By altering the structural and functional properties of the lung, prenatal exposure to tobacco smoke products and early postnatal exposure to ETS increase the likelihood of more severe complications during viral respiratory infections early in life. Martinez and collaborators (1988a) measured lung function before 6 months of age and before any lower respiratory illness in 124 infants. They found that infants with the lowest levels for various indices of airway size were three to nine times more likely to develop wheezing respiratory illnesses during the first year of life than the rest of the population. The same authors (Martinez et al., 1991) subsequently showed that, in these same infants with lower initial levels of lung function, recurrent wheezing illnesses also were more likely to occur during the first 3 years of life. A similar study performed in Australia (Young et al., 1990) confirmed that infants who present episodes of coughing and wheezing during the first 6 months of life have lower maximal expiratory flows before any such illnesses develop.

The increased likelihood of pulmonary complications during viral respiratory infections in infants of smoking parents has important long-term consequences for the affected individual. There is considerable evidence suggesting that subjects with chronic obstructive lung diseases have a history of childhood respiratory illnesses more often than subjects without such diseases (reviewed by Samet and coworkers [1983]). Burrows and collaborators (1988) found that active smokers without asthma (N = 41) who had a history of respiratory troubles before age 16 years showed significantly steeper declines in FEV_1 (as a percentage of predicted) after the age of 40 than did

nonasthmatic smokers without such a history (N = 396). Although these results may have been influenced by recall bias, they suggest that lower respiratory tract illnesses during a period of rapid lung development may damage the lung and increase the susceptibility to potentially harmful environmental stimuli.

There is no information available on the degree of reversibility of changes induced by exposure to ETS during early life. Longitudinal studies of lung function in older children have shown, however, that diminished levels of lung function are found in children of smoking parents at least until the adolescent years.

7.2.4. Exposure to ETS and Bronchial Hyperresponsiveness

Bronchial hyperresponsiveness consists of an enhanced sensitivity of the airways to pharmacologic or physical stimuli that normally produce no changes or only small decreases in lung function in normal individuals. Subjects with bronchial hyperresponsiveness have significant drops in airway conductance and maximal expiratory flows after inhalation of stimuli such as cold air, hypertonic saline, nebulized distilled water, methacholine, or histamine. Bronchial hyperresponsiveness is regarded as characteristic of asthma (O'Connor et al., 1989) and may precede the development of this disease in children (Hopp et al., 1990). It has also been considered as a predisposing factor for chronic airflow limitation in adult life (O'Connor et al., 1989).

Recent studies of large population samples have shown that active smokers have increased prevalence of bronchial hyperresponsiveness (Woolcock et al., 1987; Sparrow et al., 1987; Burney et al., 1987) when compared with nonsmokers. This relationship seems to be independent of other possible determinants of bronchial hyperresponsiveness (O'Connor et al., 1989). However, one large study of almost 2,000 subjects from a general population sample failed to find a significant relationship between smoking and prevalence of bronchial hyperresponsiveness (Rijcken et al., 1987). The subjects involved in the latter study were younger and were therefore exposed to a smaller average cumulative pack-years of smoking than were the subjects of studies in which a positive relationship was found. This suggests that the relationship may be evident only among individuals with a high cumulative exposure.

Epidemiologic studies have demonstrated that exposure to ETS is associated with an increased prevalence of bronchial hyperresponsiveness in children. Murray and Morrison (1986), in a cross-sectional study, reported that asthmatic children of smoking mothers were four times more likely to show increased responsiveness to histamine than were asthmatic children of nonsmoking mothers. O'Connor and coworkers (1987), in a study of a general population sample, found a significant association between maternal smoking and bronchial hyperresponsiveness (as assessed with eucapnic hyperpnea with subfreezing air) among asthmatic children, but not among nonasthmatic children (Weiss et al., 1985). Martinez and coworkers (1988b) reported a fourfold increase in bronchial responsiveness to carbachol among male children of smoking parents when compared with male children of parents who were both nonsmokers. A smaller (and statistically not significant) increase in bronchial responsiveness was reported in girls. These authors also found that the effect of parental smoking was stronger in asthmatic children, and results were still significant after controlling for this factor in a multivariable analysis. Because only a small

proportion of mothers in this population smoked during pregnancy, the effect was considered to be associated mainly with exposure to ETS in these children. Lebowitz and Quackenboss (1990) showed that odds of having bronchial reactivity (as assessed by the diurnal variability in maximal expiratory flow rate) were 3.6 times as high among 18 children aged 15 years and younger who lived with persons who smoked more than 20 cigarettes per day than among 62 children of the same age who lived with nonsmokers (95% C.I. = 1.2, 10.6). Children living with smokers of 1 to 20 cigarettes per day had a prevalence of bronchial reactivity that was similar to that of children living with nonsmokers.

Therefore, there is evidence indicating that parental smoking enhances bronchial responsiveness in children. The mechanism for this effect and the possible role of atopy in it are unknown. The doses required to enhance bronchial responsiveness in children exposed to ETS are apparently much lower than those required to elicit similar effects among adult active smokers. A process of self-selection, by which adults who are more sensitive to the effects of tobacco smoke do not start smoking or quit smoking earlier, may explain this finding. Variations in bronchial responsiveness with age also may be involved (Hopp et al., 1985).

Increased bronchial responsiveness may be an important predisposing factor for the development of asthma in childhood (Hopp et al., 1990). Moreover, it has been suggested that bronchial hyperresponsiveness may have effects on the developing respiratory system that predispose to chronic obstructive lung disease in later life (O'Connor et al., 1989). Redline et al. (1989) examined bronchial responsiveness to hyperventilation with cold air and its association with growth of lung function over a 12-year period in 184 children and young adults (aged 8 to 23 years) over a maximum span of 12 years. Among subjects with persistent positive responses to cold air during followup, forced vital capacity grew faster, but forced expiratory flows grew more slowly, than among subjects who consistently did not respond to cold air. Among subjects with intermittently positive cold air responses, forced expiratory flows also grew more slowly than in controls, but growth of forced vital capacity was not changed. Although this study needs confirmation, its results suggest that bronchial hyperresponsiveness may have significant effects on the rate of growth of airway function and lung size in children.

7.2.5. ETS Exposure and Atopy

Atopy has been defined epidemiologically as the presence of immediate hypersensitivity to at least one potential allergen administered by skin prick test. Atopy is an immediate form of hypersensitivity to antigens (called allergens) that is mediated by IgE immunoglobulin. Allergy (as indicated by positive skin test reactivity to allergens, high levels of circulating IgE, or both) is known to be present in almost all cases of childhood asthma. Recent epidemiologic studies have indicated that an IgE-mediated reaction may be necessary for the occurrence of almost all cases of asthma at any age (Burrows et al., 1989).

Although genetic factors appear to play a major role in the regulation of IgE production (Meyers et al., 1987; Hanson et al., 1991), several reports have indicated that active smoking significantly increases total serum IgE concentrations and may thus influence the occurrence of allergy (Gerrard et al., 1980; Burrows et al., 1981;

Zetterstrom et al., 1981; Taylor et al., 1985). Active smokers also have been found to have higher eosinophil counts and increased prevalence of eosinophilia when compared with nonsmokers (Kauffmann et al., 1986; Halonen et al., 1982; Taylor et al., 1985). The physical and chemical similarities between MS and ETS have prompted the investigation of a possible role of passive smoking in allergic sensitization in children.

Weiss and collaborators (1985) first reported a 2.2-fold increased risk of being atopic in children of smoking mothers. Martinez and coworkers (1988b) confirmed that children of smoking parents were significantly more likely to be atopic than were children of nonsmoking parents, and the researchers reported that this association was stronger for male children. They also found a rough dose-response relationship between the number of cigarettes smoked by parents and the intensity of the skin reactions to a battery of allergens. Ronchetti and collaborators (1990) extended these findings in the same population sample of Martinez and coworkers. They found that total serum IgE levels and eosinophil counts were significantly increased in children of smoking parents, and the effect was related to both maternal and paternal smoking.

It is relevant to note that, due to the so-called "healthy smoker effect," children of smokers should be genetically less sensitive than children of nonsmokers, because the latter are likely to include a disproportionate number of allergic subjects who are very sensitive to the irritant effects of smoke. As a consequence, the atopy-inducing effects of ETS may be substantially underestimated.

In summary, there is convincing evidence that both maternal smoking during pregnancy and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization. These changes elicited by exposure to tobacco products may predispose children to lower respiratory tract illnesses early in life and to asthma, lower levels of lung function, and chronic airflow limitation later in life. Most of these same effects have been described for active smoking in adults. These smoke-induced changes are, therefore, known biological mechanisms for the increased prevalence of respiratory diseases associated with ETS exposure described later in this chapter.

Exposure to tobacco smoke products during pregnancy and to ETS soon after birth may be the most important preventable cause of early lung and airway damage leading to both lower respiratory illness in early childhood and chronic airflow limitation later in life.

7.3. EFFECT OF PASSIVE SMOKING ON ACUTE RESPIRATORY ILLNESSES IN CHILDREN

A review of the literature that examined the effects of exposure to ETS on the acute respiratory illness experiences of children was contained in the Surgeon General's report on the health consequences of involuntary

Table 7-1. Studies on respiratory illness referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Surgeon General	NRC
Cameron et al. (1969)	158	Children (6 to 9)	X	
Colley (1971)	2,205	Infants	X	
Colley (1974)	1,598	Children (6 to 14)		X
Dutau et al. (1981)	892	Infants/children (0 to 6)		X
Fergusson et al. (1981)	1,265	Infants	X	X
Leeder et al. (1976)	2,149	Infants	X	X
Pedreira et al. (1985)	1,144	Infants	X	X
Pullan and Hey (1982)	130	Children (10 to 11)	X	
Rantakallio (1978)	3,644	Infants/children (0 to 5)	X	X
Speizer et al. (1980)	8,120	Children (6 to 10)	X	X
Ware et al. (1984)	8,528	Children (5 to 9)	X	

smoking (U.S. DHHS, 1986) and in the report on environmental tobacco smoke by the NRC (1986). Table 7-1 shows the studies referenced in these two reports.

The Surgeon General's report concluded that "the results of these studies show excess acute respiratory illness in children of parents who smoke, particularly in children under 2 years of age," and that "this pattern is evident in studies conducted with different methodologies and in different locales" (page 44). It estimated that the increased risk of hospitalization for severe bronchitis or pneumonia ranged from 20% to 40% during the first year of life. The report stated that "young children appear to be a more susceptible population for the adverse effects of involuntary smoking than older children and adults" (page 44). Finally, the report suggested that "acute respiratory illnesses during childhood may have long-term effects on lung growth and development, and might increase the susceptibility to the effects of active smoking and to the development of chronic lung disease" (page 44).

The 1986 NRC report observed that "all the studies that have examined the incidence of respiratory illnesses in children under the age of 1 year have shown a positive association between such illnesses and exposure to ETS. The association is very unlikely to have arisen by chance" (page 208). It pointed out that "some of the studies have

examined the possibility that the association is indirect by allowing for confounding factors . . . and have concluded that such factors do not explain the results. This argues, therefore, in favor of a causal explanation" (page 208). The report concluded that "bronchitis, pneumonia, and other lower-respiratory-tract illnesses occur up to twice as often during the first year of life in children who have one or more parents who smoke than in children of nonsmokers" (page 217).

7.3.1. Recent Studies on Acute Lower Respiratory Illnesses

Several recent studies not referenced in the Surgeon General's report or in the NRC report have addressed the relationship between parental smoking and acute lower respiratory illnesses in children (see Table 7-2).

Chen and coworkers (1986) studied 1,058 infants out of 1,163 infants born in a given period in two neighborhoods in Shanghai, People's Republic of China. Information on hospital admissions from birth to 18 months, smoking habits of household members, parental education, and social and living conditions was obtained by use of a self-administered questionnaire completed by the parents when the child reached 18 months of age. Hospital admissions were divided into those due to respiratory illness and those from all other conditions. None of the mothers in the study smoked. There was no statistically significant association between exposure to ETS and admission to the hospital for any condition other than respiratory illnesses. Compared with nonsmoking households, the risk of being admitted to a hospital for respiratory illnesses was 17% higher when one to nine cigarettes were smoked daily by household members (95% C.I. =

Table 7-2. Recent epidemiologic studies of effects of passive smoking on acute lower respiratory tract illnesses (LRIs)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Breese-Hall et al. (1984)	Cases: 29 infants hospitalized with bronchiolitis due to respiratory syncytial virus (RSV) Controls: 58 infants hospitalized for nonrespiratory conditions; 58 infants hospitalized due to LRIs not due to RSV	Parental questionnaire	See population studied	Cases vs. controls Odds ratio (OR) = 4.8 (1.8, 13.0) (>5 cig./day vs. none) LRI controls vs. non-LRI controls OR = 2.7 (1.3, 5.7)	Cases matched to controls for age, sex, race, month of admission, form of payment; selection bias not ruled out
Chen et al. (1986)	1,058 infants born in Shanghai, China	Parental self-administered questionnaire; number of cigarettes smoked by household members	Admissions to hospital for respiratory illness as reported by parents	Cig./day OR 1-9 1.2 (0.6, 2.3) >9 1.9 (1.1, 3.4)	Controlling for crowding, paternal education, feeding practices, birthweight, family history of chronic respiratory illness

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Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Chen et al. (1988)	2,227 infants born in Shanghai, China	Household self-administered questionnaire	Incidence of hospitalization for respiratory illness, incidence of bronchitis or pneumonia first 18 mo. of life	First 6 mo. of life: OR = 3.0 (1.6, 5.7); 7-18 mo. of life: OR = 1.8 (1.0, 3.2)	No smoking mothers; controlling for sex, birthweight, feeding practices, nursery care, paternal education, use of coal for cooking, family history of chronic respiratory illness
Chen (1989)	Same as above	Same as above	Same as above	First 18 mo. of life: incidence density ratio (IDR) = 1.6 for breast-fed babies; IDR = 3.4 for non-breast-fed babies; confidence intervals not calculable	

(continued on the following page)

Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
McConnochie and Roghmann (1986a)	53 infants with bronchiolitis; 106 controls	Parental questionnaire at mean age 8 yr.	See population studied	Cases vs. controls OR = 2.4 (1.2, 4.8) (smoking mother vs. nonsmoking mother)	Cases matched to controls for sex and age; controlling for family history of asthma, social status, older siblings, crowding; selection bias not ruled out
Ogston et al. (1987)	1,565 infants in New Zealand	Maternal and paternal smoking habits during pregnancy by questionnaire	Upper and lower respiratory illnesses during first year of life	Paternal smoking OR = 1.43 (1.05, 1.96); maternal smoking OR = 1.82 (1.25, 3.64)	Upper and lower respiratory illnesses not distinguished; controlling for maternal age, feeding practices, heating type, social class
Anderson et al. (1988)	102 children hospitalized in Atlanta, Georgia, <2 yr.; 199 controls	Self-reported smoking habits of family members	LRI	No effect of parental smoking after controlling for other risk factors	Selection bias possible

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Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Woodward et al. (1990)	2,125 children aged 18 mo. to 3 yr.	Self-administered mailed questionnaire	"Respiratory score" regarding 13 different symptoms; top 20% compared with low 20%	OR = 2.0 (1.3, 3.4) of having a smoking mother for high scores compared with low scores; no effect of paternal smoking	Controlling for parental history of respiratory illness, child care, parental occupation, maternal stress
Wright et al. (1991)	847 white children born in Tucson, Arizona	Self-administered questionnaire and cotinine levels in a subsample	LRIs as assessed by the infants' pediatricians	OR = 1.5 (1.1, 2.2) of having smoking mother; no effect of paternal smoking	Effects significant only for LRIs occurring in the first 6 mo. of life; controlling for day care, room sharing, parental history of respiratory illnesses, feeding practices, sex, and maternal education
Reese et al. (1992)	491 children aged 1 mo. to 17 yr.	Cotinine levels in urine of children; questionnaire of parents' current smoking	Hospitalization for bronchiolitis	Higher levels in children hospitalized for bronchiolitis than in controls ($p<0.02$)	No effects of ETS on hospitalization for asthma

[1]95% confidence intervals in parentheses.

0.6, 2.3) and was 89% higher when more than nine cigarettes were smoked daily by household members (95% C.I. = 1.1, 3.4). The authors controlled for the effects of crowding, chronic respiratory illness in the family, father's education, type of feeding, and birthweight.

Chen and coworkers (1988) subsequently studied 2,227 out of 2,315 children born in the last quarter of 1983 in Chang-Ning District, Shanghai, People's Republic of China. There were no smoking mothers in this population. The authors reported a significant linear relationship of total daily cigarette consumption by family members with incidence density of hospitalization for respiratory illness and with cumulative incidence of bronchitis and pneumonia in the first 18 months of life. The relationship was stronger for the 1- to 6-month period than for the 7- to 18-month period: When compared with households whose members did not smoke at home, the risk of being hospitalized for respiratory illness during the 1- to 6-month interval was three times as high (95% C.I. = 1.6, 5.7) in households whose members smoked more than nine cigarettes at home, whereas comparison of the same two types of household showed that the risk of being hospitalized for respiratory illness during the 7- to 18-month interval was only 1.8 times as high (95% C.I. = 1.0, 3.2) in the smoking household. The relationship also was stronger among low-birthweight infants. Results were independent of sex, birthweight, feeding practices, nursery care, paternal education, family history of chronic respiratory diseases, and use of coal for cooking.

In a different publication based on the same data from the 1988 study, Chen (1989) reported that the effects of passive smoking were stronger in artificially fed infants than in breast-fed infants. When comparing breast-fed infants of nonsmoking and smoking families, the risk of being hospitalized for respiratory illness in the first 18 months of life was 1.6 times as high for breast-fed infants of smoking families (> 19 cig./day), whereas the same risk was 3.4 times as high among non-breast-fed infants of smoking families.

The studies by Chen (1989) and Chen and coworkers (1986, 1988) were retrospective in nature and thus not immune to possible biases generated by the fact that the occurrence of the outcome event may enhance reporting or recall of the conditions considered as risk factors. However, conclusions are strengthened by the finding that admissions for nonrespiratory illnesses were unrelated to passive smoking in the study in which the relationship was assessed (Chen et al., 1986) and by the fact that the finding remained significant after adjusting for known confounders.

Breese-Hall and coworkers (1984) studied 29 infants hospitalized with confirmed RSV bronchiolitis before age 2, 58 controls hospitalized for acute nonrespiratory conditions, and 58 controls hospitalized for acute lower respiratory illnesses from causes other than RSV. Cases and controls were matched for age, sex, race, month of admission, and form of payment for hospitalization. Information on smoking habits in the family was obtained at the time of each patient's admission. Cases were 4.8 times as likely as controls (95% C.I. = 1.8, 13.0) to have one or more household members who smoked five or more cigarettes per day. However, there was no significant difference in the prevalence of cigarette smoking in the households of subjects with respiratory illnesses caused by RSV and those not caused by RSV. This was attributable to the fact that the controls with respiratory illnesses not caused by RSV were also much more likely to live with smokers of five or more cigarettes per day than were controls with nonrespiratory

illnesses (OR = 2.7, 95% C.I. = 1.3, 5.7). Little information is given about enrollment and refusals; thus, it is not possible to know if selection bias may have influenced the results. Also, other possible confounders such as socioeconomic level were not taken into account when matching cases to controls or when data were analyzed.

McConnochie and Roghmann (1986a) compared 53 infants drawn from the patient population of a group practice in Rochester, New York, who had physician-diagnosed bronchiolitis before age 2 years, with 106 controls from the same practice who did not have lower respiratory illnesses during the first 2 years of life and who were matched with cases for sex and age. Parental interviews were conducted when the child had a mean age of 8.4 years. Parents were asked about family history of respiratory conditions and allergy, socioeconomic status, passive smoking, home cooking fuel, home heating methods, and household pets. Passive smoking was defined as current and former smoking of "at least 20 packs of cigarettes or 12 ounces of tobacco while living in the home with the subject." Current and former smoking was scored equally, based on the assumption that the report of either reflected passive smoking in the first 2 years of life. Frequency of paternal smoking was not increased among children who had bronchiolitis. Cases were 2.4 times (95% C.I. = 1.2, 4.8) as likely to have smoking mothers as were controls. The association was stronger in families with older siblings (OR = 8.9); however, a multiplicative test for this interaction did not reach statistical significance. The authors studied 63% of eligible cases and 34% of eligible controls. Although the reasons for exclusion from both groups are detailed, selection bias cannot be excluded completely, and the authors give no information about maternal smoking habits among excluded subjects. Also, overreporting of smoking by parents who were aware of their child's history of bronchiolitis may have introduced biases due to differential misclassification. However, the results were consistent across groups classified according to family history of asthma or allergy, social status, presence of older siblings, and crowding.

Ogston and coworkers (1987) conducted a prospective study of 1,565 infants of primigravidae enrolled antenatally in the Tayside Morbidity and Mortality Study in New Zealand. Information on the father's smoking habits and on the mother's smoking habits during pregnancy was obtained at the first antenatal interview and from a postnatal questionnaire. A summary record was completed when the child was 1 year of age and included a report of the child's respiratory illnesses (defined as "infections of the upper or lower respiratory tract") during the first year of life derived from observations made by health visitors during scheduled visits to see the child. The authors used a multiple logistic regression to control for the possible effects of maternal age, feeding practices, heating type, and father's social class on the relationship between parental smoking and child health. Of the 588 children of nonsmokers in this sample, 146 (24.8%) had respiratory illnesses during the first year of life. Paternal smoking was associated with a 43% increase (95% C.I. = 4.7, 96.1) in the risk of having respiratory illnesses in the first year of life, and this was independent of maternal smoking. The risk of having a respiratory illness was 82% higher (95% C.I. = 25.6, 264.4) in infants of smoking mothers than in infants of nonsmoking parents. Smoking by both parents did not increase the risk of having respiratory illnesses beyond the level observed in infants with smoking mothers and nonsmoking fathers. It is difficult to compare this study with other reports on the same issue because the authors could not distinguish between upper and lower respiratory tract illnesses.

Anderson and coworkers (1988) performed a case-control study of 102 infants and young children hospitalized in Atlanta, Georgia, for lower respiratory tract illnesses before age 2 and 199 age- and sex-matched controls. The unadjusted relative odds of having any family member smoking cigarettes were 2.0 times as high ($p < 0.05$) among cases as among controls (confidence interval was not calculable from the reported data). The effect disappeared, however, after controlling for other factors (prematurity, history of allergy in the child, feeding practices, number of persons sleeping in the same room with the child, immunization of the child in the last month) in a multivariable logistic regression analysis. No information is provided in this report about maternal and paternal smoking separately, and the number of cigarettes smoked at home by each family member was not recorded either. Also, almost 30% of all target cases declined participation in the study, and no information was available on smoking habits in the families of these children. No information is given about number of refusals among controls.

Woodward and collaborators (1990) obtained information about the history of acute respiratory illnesses in the previous 12 months on 2,125 children aged 18 months to 3 years whose parents answered a questionnaire mailed to 4,985 eligible families in Adelaide, Australia. A "respiratory score" was calculated from responses to questions regarding 13 different upper and lower respiratory illnesses. A total of 1,218 parents (57%) gave further consent for a home interview. From this total, parents of 258 cases (children whose respiratory score fell in the top 20% of scores) and 231 "controls" (children whose scores were within the bottom 20% of scores) were interviewed at home. When compared with controls, cases were twice as likely to have a mother who smoked during the first year of life (95% C.I. = 1.3, 3.4). This effect was independent of parental history of respiratory illnesses, other smokers in the home, use of group child care, parental occupation, and level of maternal stress and social support. The authors found no differences in the way smokers and nonsmokers perceived or managed acute respiratory illnesses in their children. Based on this finding, they ruled out that such differences could explain their findings. They also reported that feeding practices strongly modified the effect of maternal smoking; among breast-fed infants, cases were 1.8 times as likely to have smoking mothers as were controls (95% C.I. = 1.2, 2.8), whereas among non-breast-fed infants, cases were 11.5 times as likely to have smoking mothers as were controls (95% C.I. = 3.4, 38.5).

Wright and collaborators (1991) studied the relationship between parental smoking and incidence of lower respiratory tract illnesses in the first year of life in a cohort of 847 white non-Hispanic infants from Tucson, Arizona, who were enrolled at birth and followed prospectively. Lower respiratory illnesses were diagnosed by the infants' pediatricians. Maternal and paternal smoking was ascertained by questionnaire. For verification of smoking habits, the researchers measured cotinine in umbilical cord serum of a sample of 133 newborns who were representative of the population as a whole. Cotinine was detectable in umbilical cord sera of all infants whose mothers reported smoking during pregnancy and in 7 of 100 cord specimens of infants whose mothers said they had not smoked during pregnancy. There was a strong relationship between cotinine level at birth and the amount that the mother reported having smoked during pregnancy.

Children whose fathers smoked were no more likely to have a lower respiratory tract illness in the first year of life than were children of nonsmoking fathers (31.3% vs. 32.2%, respectively). The incidence of lower respiratory

tract illnesses was 1.5 times higher (95% C.I. = 1.1, 2.2) in infants whose mothers smoked as in infants whose mothers were nonsmokers. This relationship became stronger when mothers who were heavy smokers were separated from light smokers; 45.0% of children born to mothers who smoked more than 20 cigarettes per day had a lower respiratory illness, compared with 32.1% of children whose mothers smoked 1 to 19 cigarettes per day and 30.5% of children of nonsmoking mothers ($p < 0.05$). The authors tried to differentiate the effects of maternal smoking during pregnancy from those of postnatal exposure to ETS but concluded that the amount smoked contributed more to lower respiratory tract illness rates than did the time of exposure. The authors also found that maternal smoking had a significant effect on the incidence of lower respiratory tract illnesses only for the first 6 months of life; the risk of having a first lower respiratory illness between 6 and 12 months was independent of maternal smoking habits. A logistic regression showed that the effect of maternal smoking was independent of parental childhood respiratory troubles, season of birth, day-care use, and room sharing. Feeding practices, maternal education, and child's gender were unrelated to incidence of lower respiratory illnesses in this sample and were not included in the regression. The analysis also showed a significant interaction between maternal smoking and day-care use; the effects of maternal smoking were significant when the child did not use day care (OR = 2.7; 95% C.I. = 1.2, 5.8) but were weaker and did not reach significance among infants who used day care (OR = 1.9; 95% C.I. = 0.9, 4.0). The authors suggested that day-care use may protect against lower respiratory illnesses by reducing exposure to ETS.

Reese et al. (1992) studied urinary cotinine levels in 491 children, aged 1 month to 17 years, on admission to hospital. Children admitted for bronchiolitis had higher urinary cotinine levels than a group of children of similar age admitted for nonrespiratory illnesses ($p < 0.02$). The researchers concluded that there are objective data linking passive smoking to hospital admission for bronchiolitis in infants.

7.3.2. Summary and Discussion on Acute Respiratory Illnesses

Both the literature referenced in the Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) and the additional, more recent studies considered in this report provide strong evidence that children who are exposed to ETS in their home environment are at considerably higher risk of having acute lower respiratory tract illnesses than are unexposed children. Increased risk associated with ETS exposure has been found in different locales, using different methodologies, and in both inpatient and outpatient settings. The effects are biologically plausible (see Section 7.2). Several studies also have reported a dose-response relationship between degree of exposure (as measured by number of cigarettes smoked in the household) and risk of acute respiratory illnesses. This also supports the existence of a causal explanation for the association.

The majority of studies found that the effect was stronger among children whose mothers smoked than among those whose fathers smoked. This is further evidence in favor of a causal explanation, because infants are generally in closer and more frequent contact with their mothers. There are now also fairly convincing data showing that the increased incidence of acute respiratory illnesses cannot be attributed exclusively to in utero exposure to maternal smoke. In fact, Chen (1989) and Chen and coworkers (1986, 1988) reported increased risk of acute

respiratory illnesses in Chinese children living with smoking fathers and in the total absence of smoking mothers. This effect also could be attributed either to in utero exposure to the father's smoke or to an effect on the father's sperm. This seems unlikely, however, because no such effects of parental smoking during pregnancy have been described in similar studies performed in Western countries. Furthermore, Woodward and coworkers (1990) found that children of smoking mothers were significantly more prone to acute respiratory illnesses even after mothers who smoked during pregnancy were excluded from the analysis. This clearly suggests the existence of direct effects of ETS exposure on the young child's respiratory health that are independent of in utero exposure to tobacco smoke products.

There is also convincing evidence that the risk is inversely correlated with age; infants aged 3 months or less are reported to be 3.3 times more likely to have lower respiratory illnesses if their mothers smoke 20 or more cigarettes per day than are infants of nonsmoking mothers (Wright et al., 1991). Increases in incidence of 50% to 100% (relative risks of 1.5-2.0) have been reported in older infants and young children. The evidence for an effect of ETS is less persuasive for school-age children, although trends go in the same direction as those reported for younger children. This may be due to a decrease in illness frequency, to physiological development of the respiratory tract or immune system with age, or to a decreased contact between mother and child with age.

Reasonable attempts have been made in most studies to adjust for a wide spectrum of possible confounders. The analyses indicate that the effects are independent of race, parental respiratory symptoms, presence of other siblings, socioeconomic status or parental education, crowding, maternal age, child's sex, and source of energy for cooking. One study (Graham et al., 1990) also showed that the effect of ETS exposure on proneness to acute respiratory illnesses in infancy and early childhood was also independent of several indices of maternal stress, lack of maternal social support, and family dysfunction. Other factors, such as breastfeeding, decreased birthweight, and day-care attendance, have been shown to modify the risk.

Some sources of bias may have influenced the results, but it is highly unlikely that they explain the consistent association between acute lower respiratory illness and ETS exposure. With one exception (Wright et al., 1991), all studies relied exclusively on questionnaires or interviews to assess exposure. Although questions tend to be very specific, overreporting or more accurate reporting of smoking habits by parents of affected children is possible, particularly in case-control and retrospective studies. However, such a bias should affect both respiratory and nonrespiratory outcomes, and at least two studies have shown no association between nonrespiratory outcomes and ETS exposure (Chen et al., 1988; Breese-Hall et al., 1984). Selection bias could not be excluded in some case-control studies, but satisfactory efforts were made to avoid this source of bias in most studies.

7.4. PASSIVE SMOKING AND ACUTE AND CHRONIC MIDDLE EAR DISEASES

Table 7-3. Studies on middle ear diseases referenced in the Surgeon General's report of 1986

Study	No. of subjects	Age of subjects (years)
Said et al. (1978)	3,290	10-20
Iversen et al. (1985)	337	0-7
Kraemer et al. (1983)	76	Young children (unspecified age)
Black (1985)	450	4-9
Pukander et al. (1985)	264	2-3

The Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) reviewed five studies demonstrating an excess of chronic middle ear disease in children exposed to parental cigarette smoke (Table 7-3). Both reports conclude that the data are consistent with increased rates of chronic ear infections and middle ear effusions in children exposed to ETS at home.

7.4.1. Recent Studies on Acute and Chronic Middle Ear Diseases

Several recent studies not referenced in the Surgeon General's report or in the NRC report have addressed the relationship between parental smoking and middle ear illnesses in children (Table 7-4).

Fleming and coworkers (1987) examined retrospectively risk factors for the acquisition of infections of the upper respiratory tract in 575 children less than 5 years of age. Information on smoking habits and on upper respiratory tract infections and ear infections in the 2 weeks prior to interview was obtained from the children's guardians. The authors reported a 1.7-fold increase ($p = 0.01$) in the risk of having an upper respiratory illness in children of smoking mothers when compared with children of nonsmoking mothers. This effect was independent of feeding practices, family income, crowding, day-care attendance, number of siblings aged less than 5 years, child's age, and race. The authors calculated that 10% of all upper respiratory illnesses in the population were attributable to maternal smoking, a proportion that was comparable with that attributable to day-care attendance. There was no relationship between maternal smoking and frequency of ear infections in this population sample.

Willatt (1986) studied 93 children who were the entire group of children admitted to a Liverpool hospital for tonsillectomy (considered an index of frequent upper respiratory or ear infections) during a 3-month period and 61 age- and sex-matched controls. The median age was 6.9 years (range 1.8-14.9). Parents were asked about the number of sore throats in the previous 3 months and the smoking habits of all members of the household. There was a significant

Table 7-4. Recent epidemiologic studies of effects of passive smoking on acute and chronic middle ear diseases

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Willatt (1986)	93 children aged 2-15 yr. admitted to hospital for tonsillectomy; 61 age- and sex-matched controls	Questionnaire answered by parents	Tonsillectomy	OR = 2.1 (1.1, 4.0) of having smoking mothers	Controlling for birthweight, sex, age, feeding practices, social class, crowding, sore throats in other household members
Fleming et al. (1987)	575 children <5 yr.	Questionnaire answered by child's guardian	Upper respiratory illnesses (URI) and infections in previous 2 weeks	OR = 1.7 for URI when mother smoked; no effect on ear infection	Controlling for feeding practices, income, crowding, day care, siblings, sex, race
Tainio et al. (1988)	198 Finnish newborns followed from birth to age 2.3 yr.	Questionnaire to parents	Recurrent otitis media as diagnosed by pediatricians	No effects	No distinction between maternal and paternal smoking; small sample

(continued on the following page)

Table 7-4. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Reed and Lutz (1988)	24 cases of acute otitis media; 25 controls	Questionnaire to parents	Abnormal tympanometry	OR = 4.9 (1.4, 17.2) of having smokers at home	Small sample; selection bias cannot be ruled out
Hinton (1989)	115 children aged 1-12 yr. admitted for grommet insertion; 36 controls aged 2-11 yr. in Great Britain	Questionnaire to parents	Being admitted for grommet insertion	OR = 2.1 (1.0, 4.5) of having smoking parents	No control for confounders; selection bias not ruled out
Teele et al. (1989)	877 children observed for 1 yr.; 698 observed for 3 yr.; 498 observed for 7 yr. in Boston, Massachusetts	Questionnaire to parents	Acute otitis media; number of days with middle ear effusion	13% more acute otitis during first yr. of life; more days with middle ear effusion ($p<0.009$) only during first yr.; no effects after controlling for confounders	No distinction between paternal and maternal smoking; parents smoking 1 cig./day included among smokers
Corbo et al. (1989)	1,615 children aged 6-13 yr. in Abruzzo, Italy	Questionnaire to parents	Child's snoring as reported by parents	OR = 1.8 (1.1, 3.0) for moderate smokers (1-19 cig./day); OR = 1.9 (1.2, 3.1) for heavy smokers ($\geq$20 cig./day)	No distinction between maternal and paternal smoking

(continued on the following page)

Table 7-4. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Strachan et al. (1989)	736 children in third elementary class in Edinburgh, Scotland	Salivary cotinine level	Prevalence of middle ear effusion as assessed by tympanogram	OR for doubling salivary cotinine = 1.14 (1.03, 1.27)	One-third of cases of middle ear effusion attributable to passive smoking; controlling for sex, housing tenure, social class, crowding, gas cooking, damp walls
Takasaka (1990)	77 children aged 4-8 yr. with otitis media with effusion; 134 controls matched for age and sex in Sendai, Japan	Questionnaire to parents	See population studied	No effect	Low power
Etzel et al. (1992)	132 children from day- care facility aged <3 yr.	Serum cotinine levels	Otitis media with effusion	Incidence density ratio 1.4 (1.2, 1.6) for exposed children; increases significant for ages ≤2 years only	8% of cases attributable to ETS exposure

[1]95% confidence intervals in parentheses.

relationship ($p < 0.05$) between number of episodes of sore throat and number of cigarettes smoked by the mother. The effect was independent of birthweight, sex, child's age, feeding practices, social class, crowding, and number of sore throats and tonsillectomies in other household members. The relative odds of having a smoking mother were 2.1 times as high (95% C.I. = 1.1, 4.0) in children about to undergo tonsillectomy as in children not undergoing tonsillectomy.

Tainio and coworkers (1988) followed 198 healthy newborns from birth to 2.3 years of age. The investigators recorded physician-diagnosed recurrent otitis media (defined as more than four episodes of otitis media during the first 2 years or more than four episodes during the second year). Parental smoking was more frequent (55%) among the infants with recurrent otitis media than in the comparison group (33%; $p < 0.05$). The authors comment, however, that "parental smoking was not a risk factor for recurrent otitis media," probably because there was no significant relationship between parental smoking and recurrent otitis media using definitions of the latter that differed from the one described above. No distinction was made in this study between the possible effects of maternal and paternal smoking. In addition, the study sample was probably too small to obtain reliable risk calculations.

Reed and Lutz (1988) studied 24 of 70 eligible children who had been seen in a family practice office for acute otitis media during a period of 4 months and 25 of 70 eligible children who had been seen for other reasons. Forty-five of these children had tympanograms performed and had information on household smoke exposure. Prevalence of an abnormal tympanogram (indicating the presence of middle ear effusion) was higher among children exposed to smokers at home (OR = 4.86, 95% C.I. = 1.4, 17.2). Results were independent of feeding practices, history of upper respiratory illness in the past month, low socioeconomic status, sex, age, and attendance at a day-care center. Only a small fraction of eligible subjects were included in this study, and the possibility of selection bias as an explanation for the reported results cannot be ruled out.

Hinton (1989) compared 115 children aged 1 to 12 years (mean = 5 years) admitted to a British hospital for grommet insertion with 36 children aged 2 to 11 years (mean = 6 years) with normal ears who were taken from an orthoptic clinic. Prevalence of smoking was significantly higher in parents of cases than in parents of controls (OR = 2.1, 95% C.I. = 1.0, 4.5). Potential sources of selection bias or selective misclassification cannot be determined from the data reported by the author. No effort was made to control for possible confounders.

Teele and coworkers (1989) studied consecutively enrolled children being followed in two health centers in Boston from shortly after birth until 7 years of age. Acute otitis media and middle ear effusion were diagnosed by the children's pediatricians. Data were analyzed for 877 children observed for at least 1 year, 698 children observed for at least 3 years, and 498 children observed until 7 years of age. A history of parental smoking was obtained when each child became 2 years old. A parent was considered a smoker if he or she smoked more than one cigarette per day. The child was considered exposed if either parent was a smoker. The authors reported that the incidence of acute otitis media during the first year of life was 13% higher in children of smoking parents when compared with children of nonsmoking parents ($p < 0.05$), but statistical significance was no longer present after controlling for alleged confounders (site of health care, season of birth, birthweight, socioeconomic status, presence and number of siblings,

room sharing, feeding practices, and sibling or parental history of ear infection and allergic diseases). Several of these variables may not have been confounders if they were not related to both parental smoking and incidence of acute otitis media. Controlling for risk factors that are not confounders may result in overcorrection. Parental smoking was not associated with an increased risk for acute otitis media during the first 3 years or 7 years of life. Likewise, parental smoking was associated with a significant increase in the number of days with middle ear effusion, but only during the first year of life ($p < 0.009$), and the effect was no longer present after alleged confounders were controlled for. The authors do not provide information on separate risks for maternal and paternal smoking or on the incidence of acute otitis media and middle ear effusion in children of heavy smokers.

Takasaka (1990) performed a case-control study on 201 children aged 4 to 8 in Sendai, Japan. Sixty-seven subjects had otitis media with effusion, and the remaining 134 children were a control group matched to cases by age, sex, and kindergarten class. The investigators found no significant differences in prevalence of exposure to two or more household cigarette smokers between children with and without otitis media with effusion (no information on either odds ratios or C.I.s was given). The power of this study may have been too low to determine risk factors for middle ear effusions reliably.

Corbo and coworkers (1989) examined 1,615 children aged 6 to 13 years who shared a bedroom with siblings or parents in Abruzzo, Italy. Parents were asked if the child snored and the frequency of snoring. Parents were asked about their own smoking habits; they were considered moderate smokers if the summed total for both parents was fewer than 20 cigarettes per day and heavy smokers if the summed total was 20 or more cigarettes per day. Prevalence of habitual snoring in children increased slightly with the amount of cigarettes smoked by parents; children of heavy smokers were 1.9 times as likely to be habitual snorers as children in nonsmoking households (95% C.I. = 1.2, 3.1), whereas children of moderate smokers were 1.8 times as likely to be habitual snorers as children of nonsmoking parents (95% C.I. = 1.1, 3.0). Habitual snorers were more likely to have had a tonsillectomy, but only if their parents smoked. The authors suggested that these results are plausible because adult smokers are also at increased risk of being habitual snorers.

Strachan and collaborators (1989) performed tympanograms and collected saliva for cotinine determinations in 736 children in the third primary class (ages 6½ to 7½ years) in Edinburgh, Scotland. Median of salivary cotinine concentrations was 0.19 ng/mL for 405 subjects living with no smoker, 1.8 ng/mL for 241 subjects living with one smoker, and 4.4 ng/mL for 124 subjects living with two or more smokers. For a given number of smokers in the household, girls had higher cotinine levels than boys, and children living in rented houses (i.e., of lower socioeconomic level) had higher cotinine levels than children living in houses owned by their parents. The authors found a linear relation between the logarithm of the salivary cotinine concentration and the prevalence of middle ear effusion. The authors calculated odds ratios for abnormal tympanometry relative to children with undetectable cotinine concentrations, after adjustment for sex, housing tenure (rented or owned), social class, crowding, gas cooking, and the presence of damp walls. The odds ratio for a doubling of salivary cotinine concentration was 1.14 (95% C.I. = 1.03, 1.27). At a salivary cotinine concentration of 1 ng/mL, the odds ratio of having an abnormal

tympanogram was 1.7, whereas an odds ratio of 2.3 was calculated for a cotinine level of 5 ng/mL. At least one-third of all cases of middle ear effusion may have been attributable to passive smoking.

Etzel and coworkers (1992) studied 132 children who attended a day-care facility during the first 3 years of life. The investigators measured serum cotinine levels and considered a level of 2.5 ng/mL or more to be indicative of exposure to tobacco smoke. The 87 children with serum cotinine above this level had a significantly (38%) higher rate of new episodes of otitis media with effusion during the first 3 years of life than the 45 children with lower or undetectable levels (incidence density ratio = 1.4, 95% C.I. = 1.2, 1.6). The authors calculated that 8% of the cases of otitis media with effusion occurring in this population were attributable to exposure to tobacco smoke.

7.4.2. Summary and Discussion of Middle Ear Diseases

There is some evidence suggesting that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies have failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

Available data provide good evidence demonstrating a significant increase in the prevalence of middle ear effusion in children exposed to ETS. Several studies in which no significant association was found between ETS exposure and middle ear effusion were not specifically designed to test this relationship, and, therefore, either power was insufficient or assessment of the degree of exposure was inadequate. Also, Iversen and coworkers (1985), who assessed middle ear effusion objectively, suggested that the risk associated with passive smoking increased with age. This may explain the negative results of several studies based on preschool children; the sample sizes of these studies may have been inadequate to test for increased risks of 50% or less, as would be expected in children under 6 years of age. The finding of a log-linear dose-response relationship between salivary cotinine levels and the prevalence of abnormal tympanometry in one study (Strachan et al., 1989) adds to the evidence favoring a causal link. Although not all studies adjusted for possible confounders and selection bias cannot be excluded in the case-control studies reviewed, the evidence as a whole suggests that the association is not likely to be due to chance, bias, or factors related to both ETS exposure and middle ear effusion.

The biological mechanisms explaining the association between ETS exposure and middle ear effusion require further elucidation. Otitis media with effusion is usually attributed to a loss of patency of the eustachian tube, which may be enhanced by upper respiratory infection, impaired mucociliary function, or anatomic factors (Strachan et al., 1989). It is possible that pharyngeal narrowing by adenoidal tissue (and, consequently, eustachian tube dysfunction) may be more common in these children. This is suggested by reports of a higher prevalence of maternal smoking among children about to undergo or who have undergone tonsillectomy and by an increased prevalence of habitual snoring among children of smoking parents. Impaired mucociliary clearance has been demonstrated convincingly in smoking adults (U.S. DHHS, 1984). No data are available on mucociliary transport in children exposed to ETS. However, ETS may affect mucociliary clearance in children as in adults. If this were the case and if

normal mucociliary clearance is required for rapid resolution of otitis media, exposure to ETS could result in increased prevalence of chronic middle ear effusion.

The increased prevalence of middle ear effusion attributable to ETS exposure has very important public health consequences. Middle ear effusion is the most common reason for hospitalization of young children for an operation and thus imposes a heavy financial burden to the health care system (Black, 1984). There is also evidence suggesting that hearing loss associated with middle ear effusion may have long-term consequences on linguistic and cognitive development (Maran and Wilson, 1986).

7.5. EFFECT OF PASSIVE SMOKING ON COUGH, PHLEGM, AND WHEEZING

Studies addressing the effects of passive smoking on frequency of chronic cough, phlegm, and wheezing were reviewed both in the Surgeon General's report (U.S. DHHS, 1986) and in the report by the NRC (1986) (see Table 7-5

Table 7-5. Studies on chronic respiratory symptoms referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Respiratory symptoms	Surgeon General	NRC
Bland et al. (1978)	3,105	Children/adol. (12-13)	Cough	X	X
Charlton (1984)	15,000	Children/adol. (8-19)	Cough	X	
Colley et al. (1974)	2,426	Children (6-14)	Cough	X	X
Dodge (1982)	628	Children (8-10)	Wheeze, phlegm, cough	X	X
Ekwo et al. (1983)	1,355	Children (6-12)	Cough, wheeze	X	
Kasuga et al. (1979)	1,937	Children (6-11)	Wheeze, asthma	X	
Lebowitz and Burrows (1976)	1,525	Children (<15)	Cough, phlegm, wheeze	X	X
Schenker et al. (1983)	4,071	Children (5-14)	Cough, phlegm, wheeze	X	X
Schilling et al. (1977)	816	Children/adol. (7-16)	Cough, phlegm, wheeze	X	X
Tager et al. (1979)	444	Children/adol. (5-19)	Cough, wheeze		X
Ware et al. (1984)	10,106	Children (6-13)	Cough, wheeze, phlegm		X
Weiss et al. (1980)	650	Children (5-9)	Cough, phlegm, wheeze	X	X

).

The Surgeon General's report concluded that children whose parents smoke were found to have 30% to 80% excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over sixfold among the studies reviewed. The report noted that the association with parental smoking was not statistically significant for all symptoms in all studies, but added that the majority of studies showed an increase in symptom prevalence with an increase in the number of smoking household members in the home. The report stated that the results of some studies could have been confounded by the child's own smoking habits, but noted that many studies showed a positive association between parental smoking and symptoms in children at ages before significant experimentation with cigarettes is prevalent. The report concluded that "chronic cough and phlegm are more frequent in children whose parents smoke compared to nonsmokers. The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study" (page 107).

The NRC report concluded that "children of parents who smoke compared with children of parents who do not smoke show increased prevalence of respiratory symptoms, usually cough sputum and wheezing. The odds ratios for the larger studies, adjusted for the presence of parental symptoms, were 1.2-1.8, depending on the symptoms. These findings imply that ETS exposures cause respiratory symptoms in some children" (page 216).

7.5.1. Recent Studies on the Effect of Passive Smoking on Cough, Phlegm, and Wheezing

Several recent studies not considered either in the NRC report (1986) or in the Surgeon General's report (U.S. DHHS, 1986) have addressed the relationship between passive smoking and respiratory symptoms in children (Table 7-6).

McConnochie and Roghmann (1986b) studied 223 of 276 eligible children aged 6 to 10 years without a history of bronchiolitis who were drawn from the patient population of a group practice in Rochester, New York. Information regarding the child's history of wheezing in the previous 2 years, socioeconomic status, family history of respiratory illnesses, and smoking in the household was obtained by questionnaire. Information on breastfeeding was obtained by record checks and interviews. Children whose mothers smoked were more likely to be current wheezers than were children whose mothers did not smoke (OR = 2.2, 95% C.I. = 1.0, 4.8). Neither paternal

Table 7-6. Recent epidemiologic studies of effects of passive smoking on cough, phlegm, and wheezing

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
McConnochie and Roghmann (1986b)	223 children aged 6 to 10 yr. in Rochester, New York	Parental questionnaire	Wheezing in the previous 2 yr.	OR = 2.2 (1.0, 4.8) for maternal smoking; no effect of paternal smoking	Effect disappeared after controlling for confounders; strong interaction between smoking and family history of allergy (OR = 4.5 [1.7, 12.0])
Park and Kim (1986)	3,651 children aged 0 to 14 yr. in South Korea	Questionnaire to household members	Cough in the 3 mo. prior to interview	OR = 2.4 (1.4, 4.3) for families smoking 1 to 14 cig./day; OR = 3.2 (1.9, 5.5) for families smoking $\geq$15 cig./day	Results only significant among families whose adult members did not have chronic cough

(continued on the following page)

Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Bisgaard et al. (1987)	5,953 infants enrolled at birth in Denmark	Maternal questionnaire	Episodes of wheeze during first yr. of life	OR = 2.7 (1.8, 4.0) for children whose mothers smoked ≥3 cig./day	Controlling for social status and sex; almost one-third of original sample did not participate in the study
Geller-Bernstein et al. (1987)	80 children aged 6 to 24 mo. in Israel	Parental questionnaire	Persistent wheeze as assessed by physician after 1½ yr. of followup	OR = 3.1 (1.1, 8.9) for having smoking parents	No control for parental symptoms
Cogswell et al. (1987)	100 infants of allergic parents enrolled at birth; 73 still followed at age 5 yr.	Parental questionnaire	Number of subjects who developed wheezing at different times after birth	By 5 yr., 63% of parents who smoked had wheezing children, compared with 37% of nonsmoking parents ($p<0.05$)	> one-fourth of subjects lost to followup
Toyoshima et al. (1987)	48 wheezy children <3 yr. followed in Osaka, Japan	Parental questionnaire	Number of children still wheezing at end of followup	OR = 11.8 (1.3, 105.0) for children living in smoking households	Selection bias cannot be ruled out
Tsimoyianis et al. (1987)	193 12- to 17-year-old high school athletes	Questionnaire to the child on household smoking habits	Self-report of cough, bronchitis, wheeze, and shortness of breath	No effect on bronchitis, wheeze, shortness of breath. Increased frequency of cough ($p=0.08$)	Reporting bias cannot be ruled out

(continued on the following page)

Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Andrae et al. (1988)	4,990 children aged 6 mo. to 16 yr. in Norrkoping, Sweden	Self-report of smoking by parents	Exercise-induced cough as reported by parents	OR = 1.4 (1.1, 1.8) for children whose parents smoked	No effort made to control for active smoking in older children
Somerville et al. (1988)	7,144 children aged 5 to 11 yr. in England and Scotland; 134 controls matched for age and sex in Sendai, Japan	Questionnaire answered by child's mother	Parental reports of respiratory symptoms in the child	Among English children whose parents smoked ≥20 cig./day OR = 1.6 (1.2, 2.2) of having "wheezy chest most nights"	
Rylander et al. (1988)	67 children aged 4 to 7 yr. hospitalized with respiratory syncytial virus bronchiolitis in Stockholm, Sweden	Parental questionnaire	Subsequent occasional and recurrent wheezing	Occasional wheezing OR = 4.3 (1.1, 16.4) in children of smoking parents; no effect on recurrent wheezing	Small number of subjects
Strachan (1988)	1,012 schoolchildren 6.5 to 7.5 yr. old in Edinburgh, Scotland	Parental questionnaire	Respiratory symptoms in children	No effect on wheeze; cough at night, OR = 1.6 (1.1, 2.6) in children living with one smoker; OR = 2.5 in children living with two smokers	

(continued on the following page)

Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Lewis et al. (1989)	60 cases of chronic cough aged <6 yr.; 60 controls; in Salford, United Kingdom	Parental questionnaire	See population studied	OR = 1.7 (0.8, 3.5) in children living with a smoker	Low power
Neuspiel et al. (1989)	9,670 children enrolled at birth in Great Britain	Parental questionnaire at birth, at age 5 yr. and at age 10 yr.	Wheeze between ages 1 and 10 yr.	Cumulative incidence: 5.2% mother non-smoker, 6.6% mother smoked 1 to 4 cig./day, 7.5% mother smoked 5 to 11 cig./day, 8.1% mother smoked 15 to 24 cig./day, 8.9% mother smoked >24 cig./day	Independent of sex, allergy, smoking during pregnancy, paternal smoking, crowding, dampness, feeding practices, gas cooking, social status, and maternal respiratory symptoms
Chan et al. (1989a)	134 children 7 yr. of age in London, England, <2,000 g birthweight; 123 controls with normal birthweight	Parental questionnaire	Wheeze and cough	OR = 2.7 (1.3, 5.5) of having wheeze at age 7 in children of smoking mothers, OR = 2.4 (1.3, 4.6) of having cough	Effects on wheeze independent of confounders; effects on cough disappeared after controlling for confounders

[1]95% confidence intervals in parentheses.

smoking nor total household smoking had any influence on the prevalence of wheezing. When the authors controlled for family history of respiratory allergy, direct effects of maternal smoking on prevalence of wheezing failed to reach statistical significance. However, there was a strong association between maternal smoking and wheezing among children with a positive family history of respiratory allergy (OR = 4.5, 95% C.I. = 1.7, 12.0), and the interaction between these terms was highly significant in multivariable analysis, suggesting the combined importance of both genetic factors and maternal smoking.

Park and Kim (1986) studied 3,651 children aged 0 to 14 from a randomized, clustered sample of households in South Korea (response rate: 89%). A questionnaire was administered to household members about their smoking habits and respiratory symptoms. Mothers answered questions about the presence of cough in the child in the 3 months prior to interview. The authors reported dose-response relationships between the child's cough and number of smokers in the family, number of smokers in the same room, number of cigarettes smoked by all family members, and number of cigarettes smoked by parents. The relationship was present in children of different ages (less than 5 years, 6 to 11 years, and 12 to 14 years). The authors controlled for parental education, socioeconomic status, birth rank, parental age, birth interval, number of family members, and number of siblings. Family members with cough or with morning phlegm production were significantly more likely to live with children with cough. After correcting for these two factors, chronic cough was 2.4 times as likely in children of families whose members smoked 1 to 14 cigarettes per day (95% C.I. = 1.4, 4.3) and 3.2 times as likely in children of families whose members smoked more than 15 cigarettes per day (95% C.I. = 1.9, 5.5). However, effects were more noticeable and only reached statistical significance in children of families whose adult members did not have chronic cough.

Bisgaard and coworkers (1987) studied 5,953 infants of a total of 8,423 eligible newborns (71%) enrolled in a prospective study. At the age of 1 year, the child's mother was interviewed regarding episodes of wheeze during the previous year and possible risk factors for wheezing. The risk of wheezing was 2.7 times as high (95% C.I. = 1.8, 4.0) in children whose mothers smoked three or more cigarettes per day as in children whose mothers smoked fewer than three cigarettes per day. Results were independent of social status and sex of the child. The authors decided not to control for quarter of birth or use of day-care facilities, with the assumption that these factors did not modify the relationship between maternal smoking and wheezing. Also, biases could have been introduced by the fact that almost one-third of the original sample was not included in the analysis.

Geller-Bernstein and coworkers (1987) studied 80 children aged 6 to 24 months who had been seen as outpatients or inpatients in Israel for wheezing and who had a diagnosis of atopy. The children were examined every 6 months during 4 years by a physician. At the end of assessment, the authors classified children as having "recovered" if they had been symptom-free for at least 1 (the last) year; otherwise they were classified as "persistent wheezers." "Persistent wheezers" were more likely to have smoking parents than were "recovered" children (OR = 3.1, 95% C.I. = 1.1, 8.9). This result was independent of changes in IgE levels during the study period. The authors did not control for the possible confounding effect of parental symptoms.

Cogswell and coworkers (1987) studied 100 newborns who had at least one parent with a history of hay fever or asthma. Ninety-two children were still being followed at 1 year of age and 73 at the age of 5 years. Children were examined periodically and whenever they had signs of respiratory illness. At the child's first birthday, the number of those who had developed wheezing was equally distributed between parents who did or did not smoke. By the age of 5 years, however, 62% of parents who smoked had children who had wheezed compared with 37% in nonsmoking families ($p < 0.05$). It is unlikely that these results can be explained by the confounding effect of parental symptoms, because all parents were allergic by definition. It is also quite unlikely that preferential withdrawal of nonwheezing children of smoking parents could have biased the results.

Toyoshima and coworkers (1987) from Osaka, Japan, followed 48 of 65 wheezy infants and children less than 3 years old for up to 4 years. Outcome information was obtained from charts or by telephoning the child's mother. Among 18 children who were still symptomatic 25 to 44 months after their first visit, 17 lived with smokers compared with 13 of 22 children who lived with smokers and who stopped having symptoms during followup (OR = 11.8, 95% C.I. =
1.3, 105.0). Results were independent of family history of allergy, feeding practices, and disturbances at birth. Selection bias related to the number of subjects lost for followup or with missing information could have influenced the results of this study.

Tsimoyianis and collaborators (1987) evaluated the effects of exposure to ETS on respiratory symptoms in a group of 12- to 17-year-old high school athletes (N = 193). Histories of smoking by all household members were obtained for all subjects. Athletes exposed to ETS at home were more likely to report cough than were unexposed athletes ($p = 0.08$). Frequency of bronchitis, wheeze, and shortness of breath was similar in both groups. A greater awareness of the smoking habits of those around them by subjects with cough cannot be excluded as an explanation of these findings, but this source of bias cannot explain the exposure-response trends for ETS and lung function seen in this same sample (see Section 7.8.1).

Andrae and collaborators (1988) mailed questionnaires to the parents of 5,301 children aged 6 months to 16 years living in the city of Norrkoping, Sweden. Data were obtained from 4,990 children (94% response rate). Children with parents who smoked had exercise-induced cough more often than did children of nonsmokers (OR = 1.4, 95% C.I. = 1.1, 1.8). Exposure to ETS interacted with living in houses with damage by dampness; children exposed to both had more exercise-induced cough and allergic asthma when compared to those exposed to only one or neither. Results of this cross-sectional study may have been biased by preferential reporting of symptoms by smoking parents, although a reliability study performed in a random sample was reported to confirm 95% of the answers regarding respiratory symptomatology. In addition, no effort was made to control for active smoking in older children.

Somerville and coworkers (1988) enrolled 88% of 8,118 eligible children aged 5 to 11 from England and Scotland. Data on the child's respiratory symptoms and parental smoking were obtained from a self-administered questionnaire completed by the child's mother. After exclusions for missing data, the proportions of children

available ranged from 60.9% to 63.9% of all subjects, depending on the variables involved. Logistic regression analysis was used to control for child's age, presence of siblings, one- or two-parent families, paternal employment, social class, maternal smoking during pregnancy, overcrowding, maternal education, maternal age, triceps skinfold thickness, and birthweight. For Scottish children (who were only 19% of all subjects), the authors found a significant relationship between number of cigarettes smoked at home and "chest ever wheezy" ($p < 0.01$; OR not reported). Among English children, there was a significant relationship between number of cigarettes smoked at home by mother and father together and prevalence of a wheezy or whistling chest most nights (adjusted OR in children whose parents smoked 20 cig./day = 1.6; 95% C.I. = 1.2, 2.2). Attacks of bronchitis and cough during the day or at night were also significantly correlated with number of cigarettes smoked by parents in the English sample; odds ratios in children of parents who smoked 20 cigarettes per day were 1.4 and 1.3, respectively, but no confidence intervals were reported. The authors concluded that the effect of parental smoking on respiratory symptoms in this age group is small and requires a large number of subjects to be detected.

Rylander and collaborators (1988) from Stockholm, Sweden, studied 67 children aged 4 to 7 years who had been hospitalized with virologically proven RSV infections before age 3. Questionnaires were mailed to parents regarding their smoking habits and the child's history of wheezing illnesses after the initial episode. Children who had subsequent occasional wheezing (N = 21) were more likely to have smoking parents than those (N = 24) who had no subsequent respiratory symptoms (OR = 4.3, 95% C.I. = 1.1, 16.4). However, frequency of parental smoking among children who had no subsequent respiratory symptoms was not significantly different from that of children who had subsequent recurrent wheezing. The inconsistency of the results in this study may be explained by the small number of subjects involved.

Strachan (1988) studied 1,012 of a target sample of 1,095 schoolchildren aged 6.5 to 7.5 years in Edinburgh, Scotland. Parents answered a questionnaire on their smoking habits and on respiratory symptoms in their children. There was no relationship between number of smokers in the household and prevalence of wheezing in the population. Cough at night (> 3 nights in the past month) was more likely to occur in children living with one smoker (OR = 1.6; 95% C.I. =
1.1, 2.6) or two smokers (OR = 2.5; 95% C.I. = 1.5, 4.0) than in children living with nonsmokers. Occurrence of "chesty colds" in children was also more frequent in households with one (OR = 1.3; 95% C.I. = 0.9, 1.9) or two smokers (OR = 1.9; 95% C.I. = 1.3, 3.0).

A subsequent report (Strachan et al., 1990) based on the same population sample studied the relationship between salivary cotinine levels and respiratory symptomatology in a subset of 770 children (see also Strachan et al. [1989], Section 7.4.1). The authors found no relationship between cotinine levels and wheezing or frequent night cough. Frequency of chesty colds was significantly correlated with quintals of salivary cotinine ($p < 0.01$). The authors noted that objective markers of recent exposure to ETS may not adequately reflect exposure at some critical period in the past. They also noted that there may be different ways of understanding the concept of "wheezing" and

proposed that this could explain the lack of association between this symptom and both questionnaire-based and cotinine-based assessment of exposure to ETS in their sample.

Lewis and coworkers (1989) performed a case-control study of risk factors for chronic cough in children under 6 years in Salford, United Kingdom. They enrolled 60 children referred to a pediatric outpatient clinic with cough lasting more than 2 months or frequent episodes of cough without wheeze. These 60 subjects were compared with controls admitted for routine surgical procedures. Children with chronic cough were 1.7 times (95% C.I. = 0.8, 3.5) as likely to live with a smoker as were controls. Because of the small number of subjects and the high prevalence of parental smoking (> 50%), the power of this study may have been too low to allow for meaningful conclusions.

Neuspiel and coworkers (1989) studied 9,670 of 9,953 eligible children enrolled at birth in Great Britain. Information on parental smoking was obtained at birth, at age 5 years, and at age 10 years. Outcome data were obtained from maternal interviews when the children were 10 years old. Children of smoking mothers had 11% higher risk (95% C.I. = 2%, 21%) of wheezing between ages 1 and 10 than did children of nonsmoking mothers. An exposure-response relationship was also present: Cumulative incidence was 5.2% in children whose mothers were nonsmokers, 6.6% in children whose mothers smoked 1 to 4 cigarettes per day, 7.5% in children whose mothers smoked 5 to 14 cigarettes per day, 8.1% in children whose mothers smoked 15 to 24 cigarettes per day, and 8.9% in children whose mothers smoked more than 24 cigarettes per day. The risk also was increased in children of mothers who did not smoke during pregnancy but were smokers thereafter (RR = 2.2, 95% C.I. = 1.2, 3.9). The association persisted after a logistic regression model was used to control for the effect of child's sex, child allergy, paternal smoking, parental allergy, crowding, bedroom dampness, feeding practices, gas cooking, and social status. The increase in risk was cut approximately in half but did not disappear when additional corrections for maternal respiratory symptoms and for a measure of maternal depression were made. Results of this study may be explained in part by preferential reporting of wheezy illnesses by smoking mothers. However, it is unlikely that the association between maternal smoking and wheezy illnesses found in this study can be explained exclusively by uncontrolled sources of bias; there was a striking exposure-response effect, and the association persisted after controlling for most known confounders and was independent of maternal smoking during pregnancy.

Chan and collaborators (1989a) studied 134 children aged 7 years out of 216 eligible infants of under 2,000 g birthweight who were admitted to the neonatal unit of two hospitals in London, England. Parents of these 134 children and of 123 control schoolchildren born in the same period but with normal birthweight completed a self-administered questionnaire on respiratory illnesses and on social and family history. At age 7, children whose mothers smoked were at increased risk of having frequent wheeze independent of their neonatal history (adjusted OR = 2.7; 95% C.I. = 1.3, 5.5), although the increase only reached statistical significance for children of normal birthweight. Prevalence of frequent cough was also more likely to occur in children of smoking mothers (OR = 2.4, 95% C.I. = 1.3, 4.6), and the association was significant for both cases and controls studied separately. The authors performed a logistic regression to control for possible confounders (only the low-birthweight group was included). The relationship between frequent wheeze and maternal smoking persisted among low-birthweight children after

controlling for family history of asthma, atopy, socioeconomic status, and use of neonatal oxygen. The relationship between frequent cough and maternal smoking was no longer significant among low-birthweight infants after controlling for the same possible confounders. For the low-birthweight group, the authors assessed the reliability of some of the responses to their questionnaires; there was a high correlation (r = 0.96) between the number of hospitalizations reported by parents and those documented in the outpatient clinic of the neonatal unit that followed the infants. The authors concluded that misclassification due to parental failure to recall previous respiratory illnesses in the low-birthweight group was unlikely.

Krzyzanowski and collaborators (1990) studied a sample of 298 children aged 5 to 15 who were family members of county employees enrolled in a prospective study. Parents answered a questionnaire on their smoking habits and on respiratory symptoms in their children. Indoor formaldehyde concentrations in the living environment also were measured. Prevalence rates of chronic bronchitis (as diagnosed by a physician) were significantly higher in children exposed both to ETS and to formaldehyde concentrations of over 60 parts per billion than in children with one or none of these exposures. The authors also reported that similar effects were not seen in adults.

Dijkstra and collaborators (1990) obtained consent for participation in their study for 1,051 of a total of 1,314 (80%) eligible 6- to 12-year-old schoolchildren from a rural area in The Netherlands. Parents completed a self-administered questionnaire on their smoking habits and on respiratory symptoms in their children. Complete information was available for 775 children. When compared to children of nonsmoking households, children exposed to ETS at home were significantly more likely to have cough on most days for at least 3 months consecutively (OR = 2.5, 95% C.I. = 1.1, 5.6), wheezy or whistling sounds in the chest in the last year (OR = 1.9; 95% C.I. = 1.0, 3.5), and attacks of shortness of breath with wheeze in the last year (OR = 2.0; 95% C.I. = 0.9, 4.2). Exposed children were significantly more likely to have one or more of the above symptoms than were unexposed children (OR = 2.0; 95% C.I. = 1.2, 3.7). Results were still significant after adjusting for parental respiratory symptoms and for maternal smoking during pregnancy. The authors also measured nitrogen dioxide in the homes of all children but found no association of the latter with respiratory symptoms.

Mertsola and coworkers (1991) followed prospectively for 3 months 54 patients aged 1 to 6 years from Turku, Finland, who had a history of recurrent attacks of wheezy bronchitis. The parents were told to record the symptoms of the child daily and were asked to bring their child to the hospital emergency room if the child developed signs of an acute respiratory infection. Incidence of prolonged wheezing episodes (> 4 days) during followup was significantly more likely in children exposed to ETS than in unexposed children (OR = 4.8; 95% C.I. = 1.9, 12.6). The result was independent of number of siblings, age, sex, medication, and personal history of allergy.

7.5.2. Summary and Discussion on Cough, Phlegm, and Wheezing

Recent studies reviewed in this report that were not included either in the Surgeon General's report (U.S. DHHS, 1986) or in the NRC report (1986) substantially confirm the conclusions reached in those two reports. There

is sufficient evidence for the conclusion that ETS exposure at home is causally associated with respiratory symptoms such as cough, phlegm, or wheezing in children.

The evidence is particularly strong for infants and preschool children; in this age range, most studies have found a significant association between exposure to ETS (and especially to maternal smoking) and respiratory symptoms in the children, with odds ratios generally ranging between 1.2 and 2.4. Selection bias may have influenced the results of certain cross-sectional studies; retrospective studies also may have been biased by preferential recall of their children's symptoms by smoking parents. However, the presence of a causal relationship is strongly supported by the consistency of the results for different geographic areas (Japan, Korea, People's Republic of China, Europe, and North America) and by the positive findings in prospective studies that are less subject to selection and recall biases.

In addition, efforts have been made by all researchers to control for possible confounders and to avoid sources of bias. It is not feasible for each study to take into account all possible factors that may affect the relationship under study; some of these factors may even be unknown at present. However, all reviewed studies have controlled for at least some of the best-known confounders (family history of respiratory illnesses, parental respiratory symptoms, socioeconomic status, crowding, presence of other siblings, home dampness, gas cooking, maternal level of education, perinatal problems, low birthweight, maternal age, birth rank, and maternal stress, or depression). Of these possible confounders, a history of respiratory symptoms in parents has been particularly scrutinized. The NRC report (1986) noted that bias may be introduced by parents who have a history of respiratory illnesses for several reasons. These parents may overstate their children's symptoms, or their children actually may have more respiratory illnesses and symptoms. The latter possibility could be the result of intrafamily correlation of susceptibility (referred to as familial resemblance by Kauffmann and coworkers [1989a]). Because smokers are more likely to have respiratory symptoms, one would expect that controlling for respiratory symptoms in parents would result in a decrease in statistical significance of the relationship between ETS and symptoms in the child. In fact, most recent studies that have addressed the issue report that controlling for family history of respiratory symptoms decreases but does not entirely explain the increased risk of respiratory symptoms in young children exposed to ETS. It has been stressed, however, that the use of these statistical adjustment procedures may induce an underestimation of the effect of passive smoking; this would indeed be the case if parents with symptoms (and thus more likely to be smokers) were more prone to report symptoms in their children than were parents without symptoms. Several studies also have found that the effect is independent of maternal smoking during pregnancy and cannot be attributed exclusively to intrauterine exposure to tobacco products (although the latter may potentiate the effects of postnatal exposure to ETS).

The evidence is significant but less compelling for a relationship between exposure to ETS and respiratory symptoms in school-age children. Odds ratios for this age group are usually between 1.1 and 2.0. Several studies have shown that, among school-age children, there are significant differences in susceptibility to ETS exposure between individuals. There is, in fact, evidence showing that several factors may amplify the effects of passive smoking: prematurity, a family history of allergy, a personal history of respiratory illnesses in early childhood, and

being exposed to other environmental pollutants such as formaldehyde. In addition, long-term exposure may have more important effects than short-term exposure. One study of 7-year-old children (Strachan, 1988; Strachan et al., 1990) used both questionnaires regarding smoking habits in the household and the child's saliva cotinine levels as indices of exposure to ETS. The authors found a significant increase in the risk of having frequent cough when the questionnaire was used to ascertain exposure, but no association between saliva cotinine levels and frequency of cough. As the authors remarked, biochemical markers permit characterization of recent tobacco smoke exposures, but they may not adequately reflect exposure at some critical period in the past. Recent studies of intraindividual variability of cotinine levels also have suggested that it may be misleading to assess the validity of questionnaire measures against a single determination of a biologic marker (Coultas, 1990b; Idle, 1990). It is thus possible that associations evaluated with salivary cotinine are likely to underestimate the true relationship between passive smoking and respiratory morbidity (Strachan et al., 1990).

In the case of older children who may have started experimenting with cigarettes, the confounding effects of active smoking need to be considered. Most researchers have been aware of this problem and have attempted to control for it. A great difficulty lies in misclassification of smokers due to underreporting. Young persons may be reluctant to admit smoking cigarettes. Data are often obtained from parents, who may not be aware of the child's smoking.

In summary, this report concludes that ETS exposure at home causes increased prevalence of respiratory symptoms in infants and young children. There is also good evidence indicating that passive smoking causes respiratory symptoms in some older children, particularly in children who have predisposing factors that make them more susceptible to the effects of ETS.

7.6. EFFECT OF PASSIVE SMOKING ON ASTHMA

Studies addressing the effects of passive smoking on frequency of asthma were directly reviewed only in the Surgeon General's report (U.S. DHHS, 1986) and not explicitly in the report on environmental tobacco smoke by the NRC (1986). The Surgeon General's report concluded that epidemiologic studies of children had shown no consistent relationship between the report of a doctor's diagnosis of asthma and exposure to involuntary smoking. The report pointed out that, although one study had shown an association between involuntary smoking and asthma (Gortmaker et al., 1982), others had not (Schenker et al., 1983; Horwood et al., 1985). This variability was attributed to differing ages of the children studied, differing exposures, or uncontrolled bias. The report also concluded that maternal cigarette smoking may influence the severity of asthma. Alteration of nonspecific bronchial responsiveness was proposed as a mechanism for this latter effect.

7.6.1. Recent Studies on the Effect of Passive Smoking on Asthma in Children

Several new cross-sectional and longitudinal studies published after the U.S. Surgeon General's report (U.S. DHHS, 1986) was released have addressed the relationship between frequency, incidence, and severity of asthma and

parental cigarette smoke (Table 7-7). (Studies on the relationship between ETS exposure and bronchial responsiveness were reviewed in Section 7.2.4.)

Burchfield and coworkers (1986) studied 3,482 nonsmoking children and adolescents ages 0 to 19 years out of 4,378 eligible subjects from Tecumseh, Michigan. Subjects or their parents (for children aged 15 years or younger) answered questionnaires on past history of asthma and other respiratory conditions. Information on parental smoking habits was obtained from each parent. Prevalence rates of asthma were higher among children whose parents both had smoked during the child's lifetime than among children whose parents had never smoked. The effect was stronger and only reached statistical significance for males (OR for boys = 1.7, 95% C.I. = 1.2, 2.5 in boys; OR for girls = 1.2, 95% C.I. = 0.8, 1.9). Children with one parental smoker were not more likely to have asthma than was the unexposed reference group. When results were stratified by parental history of respiratory conditions, there was some reduction in the magnitude of the parental smoking effects, but results remained significant for asthma in males. Results were also independent of age, parental education, family size, a diagnosis of hay fever, and a history of other allergies. Reporting bias and diagnostic bias may in part explain the relationships reported in this study; smoking parents may be more likely to report asthma in their children, and physicians may be more prone to diagnose asthma in children of smoking parents.

D. Evans and coworkers (1987) studied 191 out of 276 children aged 4 to 17 years from low- income families who were receiving health care for physician-diagnosed asthma in New York. Excluded children were younger and had fewer emergency room visits for asthma than those with complete data. The authors suggested that the latter subjects had more severe asthma than the general community population of low-income children with asthma. Emergency room visits and hospitalizations for asthma were assessed by reviewing hospital records. Passive smoking by the child was measured by asking one parent if he or she or anyone else in the house smoked. Authors did not differentiate between maternal and paternal smoking; no attempt was made to assess the degree of exposure to cigarette smoke. Eight children who were active smokers were excluded. There was a significant correlation between number of emergency room visits and cigarette smoke exposure ($p = 0.008$); the mean frequency ($\pm$ SD) of annual emergency room visits observed for children exposed to passive smoking was 3.1 ± 0.4, compared with 1.8 ± 0.3 for children from nonsmoking households. Passive smoking had no effect on either the frequency of days with asthma symptoms or on the annual frequency of hospitalizations. Results were

Table 7-7. Recent epidemiologic studies of effects of passive smoking on asthma in childhood

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Burchfield et al. (1986)	3,482 nonsmoking children 0 to 19 yr. in Tecumseh, Michigan	Questionnaire answered by subjects or parents	Prevalence of asthma	OR = 1.7 (1.2, 2.5) for boys; OR = 1.2 (0.8, 1.9) for girls	Independent of parental respiratory illness, age, parental education, family size, and allergies
D. Evans et al. (1987)	191 children aged 4 to 17 yr. in New York, New York	Parental questionnaire	Emergency room visits and hospitalizations for asthma (from medical records)	3.1 ± 0.4 vs. 1.8 ± 0.3 (p=0.008) emergency room visits in children of smoking and non-smoking parents	No distinction made between maternal and paternal smoking; independent of race and parental employment status
O'Connor et al. (1987)	292 subjects aged 6 to 21 yr. in Boston, Massachusetts	Parental questionnaire	Bronchial response to cold air	Significantly increased response in asthmatics whose mothers smoked	No increase in nonasthmatics whose mothers smoked

(continued on the following page)

Table 7-7. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Murray and Morrison (1989)	415 children aged 1 to 17 yr. with asthma in Vancouver, Canada	Parental questionnaire	Asthma symptom score for severity of asthma	Higher scores ($p<0.01$) in children of smoking mothers	Stronger effect in boys and older children
Krzyzanowski et al. (1990)	298 children aged 5 to 15 yr. in Tucson, Arizona	Parental questionnaire	Parental reports of asthma in their children	OR = 9.0 (2.4, 34.0) for children exposed to ETS and formaldehyde vs. nonexposed	Small sample
Sherman et al. (1990)	770 children aged 5 to 9 yr. followed for 11 yr. in Boston, Massachusetts	Parental and subject questionnaire	Physician diagnosis of asthma	No effect of parental smoking on prevalence or incidence of asthma	No effort to assess effect of heavy smoking by parents; no control for socioeconomic status
Weitzman et al. (1990)	4,331 children aged 0 to 5 yr. (U.S. National Health Interview Survey)	Maternal questionnaire	Asthma for at least 3 mo. at time of questionnaire	OR = 2.1 (1.3, 3.3) for children whose mothers smoked $\geq$10 cig./day	Independent of race, sex, family size, presence of both parents, and number of rooms

(continued on the following page)

Table 7-7. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Oldigs et al. (1991)	11 asthmatic children	Direct exposure to ETS for 1 hour	Changes in lung function	No effect	No assess-ment of effect of chronic exposure
Martinez et al. (1992)	774 children aged 0 to 5 yr. followed for several years in Tucson, Arizona	Parental questionnaire	Physician diagnosis of asthma	OR = 2.5 (1.4, 4.6) for children of low maternal education whose mothers smoked ≥10 cig./day	No effect among children of better educated mothers
Ehrlich et al. (1992)	228 children; 72 with acute asthma; 35 with nonacute asthma and 121 controls	Cotinine levels in urine of children; smoking by maternal caregiver	Emergency room and asthma clinic visits	Higher levels of cotinine in asthmatics OR = 1.9 (1.0, 3.4)	Similar cotinine levels in acute and nonacute asthmatics

[1]95% confidence intervals in parentheses.

independent of ethnicity and parental employment status. The association could have been explained by lower compliance with prescribed treatment of their children's asthma by smoking parents, but the authors found no significant differences in compliance (as assessed by an index of asthma self-management activities) between smoking and nonsmoking parents. The authors estimated that the additional cost for emergency care for asthma was $92 ± $68 per family per year.

O'Connor and coworkers (1987) performed bronchial challenges with subfreezing air in 292 subjects 6 to 21 years of age. They were selected from 879 eligible subjects of the same age who were participating in a longitudinal study on respiratory illnesses in East Boston. An attempt was made to include as many subjects as possible who reported a history of asthma or wheezing on standardized questionnaires. Therefore, the latter group of subjects were overrepresented among those tested. The change in FEV_1 caused by subfreezing air was significantly higher in asthmatic subjects whose mothers smoked at least one cigarette per day than in those whose mothers were nonsmokers. This relationship was independent of age, sex, height, personal smoking, paternal smoking, atopy, and baseline lung function. There was no relationship between maternal smoking and response to cold air among nonasthmatics.

Murray and Morrison (1989) studied 415 nonsmoking children aged 1 to 17 years consecutively referred to an allergy clinic in Vancouver, Canada, for asthma or recurrent wheezing of the chest. Questionnaires were administered to the parents of all children at the time of their first visit. Forced expiratory flows and bronchial reactivity to histamine also were measured. An asthma symptom score was calculated for each subject based on the severity of asthma and the need for medication, as reported by parents. Children of smoking mothers had significantly higher indices of asthma severity ($p < 0.01$) and significantly lower FEV_1 (84.4% predicted vs. 77.3% predicted, $p < 0.01$) than did children of nonsmoking mothers. They were also significantly more responsive to histamine than were children of nonsmoking mothers ($p = 0.01$). The effect was present in both genders but was stronger for boys than for girls. Also, the effect was stronger for older children (12 to 17 years of age) than for children 6 years of age or younger. The authors also reported a positive correlation between length of exposure to ETS and asthma symptom score. It is unlikely that these results can be explained by parental overreporting because the association between passive smoking and severity of symptoms paralleled that between passive smoking and objective measurements of severity.

In their previously reviewed report (Section 7.5.1), Krzyzanowski and coworkers (1990) found that children exposed to ETS and to more than 60 ppb of formaldehyde had significantly higher prevalence rates of asthma than those exposed to only one of these contaminants or to none (OR for the latter comparison = 9.0; 95% C.I. = 2.4, 34.0). No such association was seen among adult household members. It is unlikely that this association is attributable to parental overreporting of asthma because the authors relied on objective measurement of indoor formaldehyde concentrations.

Sherman and collaborators (1990) reported on the results of a longitudinal study of determinants of asthma in a sample of 770 schoolchildren enrolled in East Boston in 1974. Questionnaires were used to obtain data on

respiratory symptoms and illnesses, cigarette smoking history of parents and children, and household demographics. They were administered on entry and for 11 consecutive years (1978-1988). Parents answered for children aged 9 or less, except for questions on the child's smoking history. The authors identified risk factors for the onset of asthma, the occurrence of which antedated the time of first diagnosis of asthma. There was no significant relationship between maternal smoking and either prevalence of asthma at the first survey or incidence of new cases of asthma during followup (sex-adjusted RR = 1.1; 95% C.I. = 0.7, 1.7). The authors considered it unlikely that this finding could be due to exposure levels too low to increase the risk of asthma. However, no effort was made to assess the relationship between incidence of asthma and number of cigarettes smoked by parents. Likewise, no effort was made to determine the possible role of factors known to modify exposure to ETS such as parental socioeconomic level (Strachan et al., 1989).

Weitzman and coworkers (1990) studied 4,331 children aged 0 to 5 years who were part of the U.S. National Health Interview Survey. Children were categorized as having asthma if their parents reported that asthma was current at the time of interview and had been present for more than 3 months. Mothers were asked about their smoking habits during and after pregnancy. Odds of having asthma were 2.1 times as high (95% C.I. = 1.3, 3.3) among children of mothers who smoked 10 or more cigarettes per day than among children of nonsmoking mothers. The risk of having asthma was not significantly increased in children of mothers who smoked fewer than 10 cigarettes per day. Use of asthma medication was also more frequent among children of mothers who smoked 10 or more cigarettes per day (OR = 4.1; 95% C.I. = 1.9, 8.9). Results did not change significantly after controlling for gender, race, presence of both parents, family size, and number of rooms in the households. No information was available on parental respiratory symptoms or socioeconomic status. The results of this study could be explained partially by overreporting of asthma by smoking mothers.

Oldigs and collaborators (1991) exposed 11 asthmatic children to ETS and to ambient air for 1 hour. They found no significant difference in lung function or in bronchial responsiveness to histamine after ETS exposure when compared with sham exposure. The study was designed only to determine if acute exposures to ETS caused immediate effects, and it did not assess the changes induced by chronic exposure to ETS.

Martinez and coworkers (1992) studied incidence of new cases of asthma in a population sample of 774 out of 786 eligible children aged 0 to 5 years enrolled in the Tucson study of chronic obstructive lung disease. At the time of enrollment, the child's parents answered standardized questionnaires about personal respiratory history and cigarette smoking habits. Surveys were performed on an approximately yearly basis, and parents were asked if the child had been seen by a doctor for asthma in the previous year. There were 89 (11.5% of the total) new cases of asthma during followup. Children of mothers with 12 or fewer years of formal education and who smoked 10 or more cigarettes per day were 2.5 times as likely (95% C.I. = 1.4, 4.6) to develop asthma as were children of mothers with the same education level who did not smoke or who smoked fewer than 10 cigarettes per day. This relationship was independent of self-reported symptoms in parents. Decrements in lung function paralleled the increase in asthma

incidence. No relationship was observed between maternal smoking and asthma incidence among children of mothers with more than 12 years of formal education.

Ehrlich et al. (1992) studied 72 children with acute asthma recruited in the emergency room; 35 nonacute asthmatic children from an asthma clinic; and 121 control children without asthma from the emergency room. They assessed exposure to ETS both by questionnaire and by measurement of urinary levels of cotinine/creatinine ratios. Smoking by maternal caregiver was significantly more prevalent among asthmatic children (OR = 2.0, 95% C.I. = 1.1, 3.4). This was confirmed by a significant difference between groups in prevalence of cotinine to creatinine ratio of greater or equal to 30 ng/mg (OR = 1.9; 95% C.I. = 1.0, 3.4). There was no difference in exposure indices between acute and nonacute asthmatics. The authors concluded that smoking by a maternal caregiver was a significant risk factor for clinically significant asthma in children.

7.6.2. Summary and Discussion on Asthma

There is now sufficient evidence to conclude that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease. Several studies have found that bronchial responsiveness is more prevalent and more intense among asthmatic children exposed to maternal smoke. Emergency room visits are more frequent in children of smoking mothers, and these children also have been found to need more medication for their asthma than do children of nonsmoking mothers (see Table 7-4).

A simple bronchospastic effect of cigarette smoke is probably not responsible for the increased severity of symptoms associated with passive smoking because acute exposure to ETS has been found to have little immediate effect on lung function parameters and airway responsiveness in asthmatic children. Therefore, the mechanisms by which passive smoking enhances asthma in children who already have the disease are likely to be similar to those responsible for inducing asthma and entail chronic exposure to relatively high doses of ETS (see discussion below). Murray and Morrison (1988) reported that ETS exposure decreased lung function and increased medication requirements in asthmatic children only during the cold, wet season and not during the dry, hot season in Vancouver, Canada. These seasonal differences may be at least partly explained by the finding by Chilmonczyk and collaborators (1990) that urine cotinine levels of children exposed to ETS are significantly higher in winter than in summer. These seasonal fluctuations also suggest that the effects of passive smoking on asthma severity are reversible and that decreasing exposure to ETS could prevent many asthmatic attacks in affected children.

New evidence available since the Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) also indicates that passive smoke exposure increases the number of new cases of asthma among children who have not had previous episodes (see Table 7-7 for results and references). Although most studies are based on parental reports of asthma, it is highly unlikely that the relationship between asthma and ETS exposure is entirely attributable to reporting bias. In fact, concordance in the relationship between ETS exposure and both questionnaires and objective parameters such as lung function or bronchial provocation tests has been reported in several studies. The association is also biologically plausible; the mechanisms that are likely to be involved in the relationship between ETS exposure

and asthma have been discussed extensively in Section 7.2. The consistency of all the evidence leads to the conclusion that ETS is a risk factor for inducing new cases of asthma. The evidence is suggestive of a causal association but is not conclusive.

Data suggest that levels of exposure required to induce asthma in children are high; in fact, most recent and earlier studies that classified children as exposed to ETS if the mother smoked one cigarette or more usually failed to find any effect of ETS on asthma prevalence or incidence. Furthermore, two recent large studies found an increase in the prevalence (Weitzman et al., 1990) or incidence (Martinez et al., 1992) of asthma only if the mother smoked 10 cigarettes or more per day. It is also important to consider that, for any level of parental smoking, exposure to ETS is higher in children belonging to families of a lower socioeconomic level (Strachan et al., 1989) and that the relationship of maternal smoking to asthma incidence may be stronger in such families (Martinez et al., 1992). Concomitant exposure to other pollutants also may enhance the effects of ETS (Krzyzanowski et al., 1990).

7.7. ETS EXPOSURE AND SUDDEN INFANT DEATH SYNDROME

The relationship between ETS exposure and sudden infant death syndrome (SIDS) was not addressed in either the Surgeon General's report (U.S. DHHS, 1986) or in the NRC report (1986). Because of the importance of this syndrome as a determinant of infant mortality and because of the available evidence of an increased risk of SIDS in children of smoking mothers, the issue has been added to this report (Table 7-8).

SIDS is the most frequent cause of death in infants aged 1 month to 1 year. Approximately 2 of every 1,000 live-born infants (more than 5,000 in the United States alone each year) die suddenly and unexpectedly, usually during sleep, and without significant evidence of fatal illness at autopsy (CDC, 1989b). The cause or causes of these deaths are unknown. The most widely accepted hypotheses suggest that some form of respiratory failure is involved with most cases of SIDS.

In 1966, Steele and Langworth (1966) first reported that maternal smoking was associated with an increased incidence of SIDS. They studied the hospital records of 80 infants who had died of SIDS in Ontario, Canada, during 1960-1961 and compared them with 157 controls matched for date of birth, sex, hospital at which the child was born, and parity of the mother. Infants of mothers who smoked 1 to 19 cigarettes per day were twice as likely (OR = 2.1; 95% C.I. = 1.1, 3.8) to die of SIDS as were infants of nonsmoking mothers. The odds ratio was 3.6 (95% C.I. = 1.7, 7.9) when infants of mothers who smoked 20 or more cigarettes per day were compared to infants of nonsmoking mothers. The authors reported that the risk of dying of SIDS was higher in low-birthweight infants whose mothers smoked when compared with low-birthweight infants whose mothers did not smoke. However, they made no effort to control for other confounders that were related both to maternal smoking and to SIDS, such as maternal age and socioeconomic status. In addition, they made no reference to the relative roles of in utero exposure to tobacco smoke products and postnatal ETS exposure.

Naeye and collaborators (1976) studied 59,379 infants born between 1959 and 1966 in participating hospitals from several U.S. cities. After meticulous investigation of clinical and postmortem material, they identified

125 of these infants (2.3 per 1,000 live births) as having died of SIDS and compared them with 375 infants matched for place of birth, date of delivery, gestational age, sex, race, and socioeconomic status. Infants of mothers who smoked were more than 50% more likely (OR = 1.6; 95% C.I. = 1.0, 2.4) to die of SIDS than were those of mothers who denied smoking. When compared with the latter, infants of mothers who smoked six or more cigarettes per day were 2.6 times more likely (95% C.I. = 1.7, 4.0) to die of SIDS. The authors made no attempt to distinguish between in utero exposure to tobacco smoke products and ETS exposure after birth.

Bergman and Wiesner (1976) selected 100 well-defined cases of SIDS occurring in white children in King County, Washington. These cases were matched for race, sex, and birth date with 100 controls. Questionnaires were mailed to the mothers of cases and controls, but only 56

Table 7-8. Epidemiologic studies of effects of passive smoking on incidence of sudden infant death syndrome (SIDS)

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
Steele and Langworth (1966)	80 infants who died of SIDS; 157 matched controls in Ontario, Canada	Maternal report from hospital record at birth	OR = 2.1 (1.1, 3.8) when mother smoked 1 to 19 cig./day; OR = 3.6 (1.7, 7.9) when mother smoked ≥20 cig./day	No control for socio-economic status or maternal age
Naeye et al. (1976)	59,379 infants born in several U.S. cities	Maternal report from hospital record at birth	OR = 1.6 (1.0, 2.4) for any maternal smoking; OR = 2.6 (1.7, 4.0) for mothers smoking ≥6 cig./day	Controlling for place of birth, date of delivery, gestational age, sex, race, and socioeconomic status
Bergman and Wiesner (1976)	100 cases of SIDS; 100 matched controls in King County, Washington	Maternal question-naire answered after death (or at equivalent age for controls)	OR = 2.4 (1.2, 4.8); effect only significant for mothers ≤25 yr. (OR = 4.4 [1.7, 11.2])	Independent of maternal education, race, sex, and birth date
Lewak et al. (1979)	44 cases of SIDS	Maternal questionnaire	OR = 4.4 (2.1, 9.2)	No control for possible confounding factors
Malloy et al. (1988)	305,000 births in Missouri	Maternal reports on birth certificate	OR = 1.8 (1.4, 2.2)	Controlling for marital status, maternal age, education, parity, and birthweight

(continued on the following page)

Table 7-8. (continued)

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
Hoffman et al. (1988)	800 SIDS cases; 1,600 controls (NICHD cooperative study)	Maternal questionnaire	OR = 3.4 ($p<0.005$)	Controlling for age, birthweight, and race
Haglund and Cnattingius (1990)	279,000 births in Sweden	Maternal questionnaire	OR = 1.8 (1.2, 2.6). Heavy-smoking mother: OR = 2.7 (1.9, 3.9)	Independent of birthweight, maternal age, social status, parity, sex, and type of birth
Mitchell et al. (1991)	162 SIDS cases; 3 to 4 times as many controls	Parental questionnaire	Cig./day OR 1 to 9 1.9 (1.0, 3.5) 10 to 19 2.6 (1.5, 4.7) ≥20 5.1 (2.9, 9.0)	Independent of prenatal care, maternal age, education, marital status, sex, neonatal problems, parity, birthweight, race, season of death, and breastfeeding

[1]95% confidence intervals in parentheses.

cases and 86 controls returned them. Mothers who did not respond tended to be younger and poorer. A higher proportion of mothers of SIDS victims smoked cigarettes during pregnancy (61% vs. 42%). Infants of mothers who smoked after delivery were 2.4 times as likely (95% C.I. = 1.2, 4.8) to die of SIDS as were infants of nonsmoking mothers. The relationship between postnatal exposure to ETS and SIDS was significantly stronger and only reached statistical significance for mothers aged 25 years or less (OR = 4.4; 95% C.I. = 1.7, 11.2). Infants of mothers aged 25 years or less who smoked 20 or more cigarettes per day were 7.7 times as likely to die of SIDS (95% C.I. = 1.7, 35.4) as were infants of nonsmoking mothers. Effects were independent of maternal education. The authors did not try to determine the independent effects of prenatal and postnatal exposures to maternal smoking on the incidence of SIDS.

Lewak and coworkers (1979) studied all infants who died during the first year of life and who were enrolled in a health plan in Oakland, California. Using predefined criteria, they classified 44 infants (2.3 per 1,000 live births) as having died of SIDS and compared them with the rest of the population for several possible risk factors for SIDS. Mothers of infants who died of SIDS were 4.4 times (95% C.I. = 2.1, 9.2) as likely to be smokers as mothers of infants who survived. Paternal smoking had no significant influence on SIDS frequency. The authors made no effort to control for possible confounding factors, nor did they discriminate between the possible roles of prenatal and postnatal exposure to tobacco smoke products.

Malloy and coworkers (1988) linked birth and death certificates to study possible risk factors for neonatal and postneonatal mortality in over 305,000 singleton white live births in Missouri. They identified 372 infants whose deaths were attributed to SIDS (1.2 per 1,000 live births). Infants whose mothers smoked were 1.8 times as likely (95% C.I. = 1.4, 2.2) to die of SIDS than were infants of nonsmoking mothers. This relationship was independent of maternal marital status, education level, age, parity, and child's birthweight. There were no data available that would have allowed one to differentiate the effects of prenatal and postnatal exposure to tobacco smoke products.

Hoffman and collaborators (1988) reported on the results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome risk factors. They studied 800 SIDS cases and 1,600 control infants collected at six study centers across the United States. Control infants were matched for age only (N = 800) or for age, low birthweight, and race (N = 800). SIDS cases were 3.8 and 3.4 times as likely to have smoking mothers as the first and second control groups mentioned earlier, respectively ($p < 0.005$ for both comparisons). There were no data on prenatal and postnatal exposure to tobacco smoke products.

Haglund and Cnattingius (1990) examined risk factors for SIDS in a prospective study based on more than 279,000 Swedish infants who survived the first week of life. SIDS was reported as the sole cause of death in 190 infants (0.7 per 1,000), and in most cases the diagnosis was confirmed by the results of an autopsy. Infants of mothers who smoked one to nine cigarettes per day were 1.8 times as likely (95% C.I. = 1.2, 2.6) to die of SIDS as were infants of nonsmoking mothers. Infants of mothers who were heavy smokers had an even higher risk (OR = 2.7; 95% C.I. = 1.9, 3.9) of dying of SIDS, suggesting an exposure-response relationship. These findings were

independent of birthweight, maternal age, social situation, parity, sex, and type of birth. No information was available regarding smoking in the household by either mother or father after the infant's birth.

Mitchell and coworkers (1991) studied SIDS cases occurring in several health districts in New Zealand between November 1, 1987, and October 31, 1988. After careful assessment of the material available from necropsy, 162 infants were classified as having died of SIDS (3.6 per 1,000 live births). These cases were matched for age with three to four times as many controls. The researchers interviewed the parents and obtained complete information for 128 cases and 503 controls. Information on maternal smoking during pregnancy (as a yes/no variable) was obtained from the obstetric records, whereas information on number of cigarettes smoked by the mother in the 2 weeks preceding the interview was obtained from questionnaires. Mothers of infants who died of SIDS were 3.3 times as likely (95% C.I. = 2.2, 5.0) to smoke during pregnancy as were mothers of controls. The analysis of the relationship between maternal smoking after the child's birth and frequency of SIDS showed clear evidence of a biological gradient of risk. Odds ratios were as follows: 1.9 (95% C.I. = 1.0, 3.5) for mothers who smoked 1 to 9 cigarettes per day; 2.6 (95% C.I. = 1.5, 4.7) for mothers who smoked 10 to 19 cigarettes per day; and 5.1 (95% C.I. = 2.9, 9.0) for mothers who smoked 20 or more cigarettes per day. The association between maternal smoking and SIDS frequency was independent of antenatal care, maternal age, maternal education, marital status, sex, neonatal problems, parity, socioeconomic status, birthweight, gestational age, race, season of death, sleep position at death, and breastfeeding.

In summary, there is strong evidence that infants whose mothers smoke are at increased risk of dying suddenly and unexpectedly during the first year of life. This relationship is independent of all other known risk factors for SIDS, including low birthweight and low gestational age. The finding that there is a biological gradient of risk extending from nonsmoking mothers to those smoking more than 20 cigarettes per day adds to the evidence that exposure to cigarette smoke products is involved in the sequence of events that result in SIDS. Available studies cannot differentiate the possible effects with respect to SIDS of exposure to tobacco smoke products in utero from those related to passive smoking after birth. As explained earlier (Section 7.2.2), both human and animal studies show that maternal smoking during pregnancy may modify and potentiate the effects of postnatal ETS exposure. The relationship between maternal smoking and SIDS is independent of low birthweight, which is the most important known effect of maternal smoking during pregnancy. In addition, the incidence of SIDS is apparently associated with days of higher air pollution levels (Hoppenbrouwers et al., 1981), which could indicate a direct effect of airborne contaminants.

In view of the fact that the cause of SIDS is still unknown, it is not possible to assess the biological plausibility of the increased incidence of SIDS related to ETS exposure. Consequently, at this time this report is unable to assert whether or not passive smoking is a risk factor for SIDS.

7.8. PASSIVE SMOKING AND LUNG FUNCTION IN CHILDREN

The Surgeon General's report (U.S. DHHS, 1986) reviewed 18 cross-sectional and longitudinal studies on the effects of ETS exposure on lung function in children (Table 7-9

Table 7-9. Studies on pulmonary function referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Surgeon General	NRC
Berkey et al. (1986)	7,834	Children (6 to 10)	X	X
Brunekreef et al. (1985)	173	Adult women	X	
Burchfield et al. (1986)	3,482	Infants/children (0 to 10)	X	
Chen and Li (1986)	571	Children/adol. (8 to 16)	X	X
Comstock et al. (1981)	1,724	Adults	X	
Dodge (1982)	558	Children (8 to 10)	X	X
Ekwo et al. (1983)	1,355	Children (6 to 12)	X	
Ferris et al. (1985)	10,000	Children/adol. (6 to 13)		X
Hasselblad et al. (1981)	16,689	Children (5 to 17)	X	X
Kauffmann et al. (1983)	7,818	Adults	X	
Kentner et al. (1984)	1,851	Adults	X	
Lebowitz (1984)	117	Families	X	
Lebowitz and Burrows (1976)	271	Children/adol. (<16)	X	X
Schilling et al. (1977)	816	Children/adol. (<18)	X	X
Tager et al. (1979)	444	Children (5 to 19)		X
Tager et al. (1983)	1,156	Children (5 to 9)	X	X
Tashkin et al. (1984)	1,080	Children (7 to 17)	X	X
Vedal et al. (1984)	4,000	Children (6 to 13)	X	
Ware et al. (1984)	10,106	Children (6 to 13)		X
Weiss et al. (1980)	650	Children (5 to 9)	X	X
White and Froeb (1980)	2,100	Adults	X	

). The report concluded that "the available data demonstrate that maternal smoking reduces lung function in young children" (page 54). The hypothesis was proposed that passive smoking during childhood, by affecting the maximal level of lung function attainable during early adult life, may increase the subsequent rate of decline of lung function and, thus, increase the risk of chronic obstructive lung disease.

The NRC report (1986) reached similar conclusions after reviewing 12 articles (Table 7-9). The authors' summary asserted that "estimates of the magnitude of the effect of parental smoking on FEV_1 function in children range from 0 to 0.5% decrease per year. This small effect is unlikely by itself to be clinically significant. However, it may reflect pathophysiologic effects of exposure to ETS in the lungs of the growing child and, as such, may be a factor in the development of chronic airflow obstruction in later life" (page 215).

7.8.1. Recent Studies on Passive Smoking and Lung Function in Children

Studies appearing since the 1986 reports are presented in Table 7-10.

Lung function measurements were included in the cross-sectional study by O'Connor and collaborators (1987) described earlier (Section 7.6.1). When compared to 97 nonasthmatic children of nonsmoking mothers (mean age ± SEM = 12.8 ± 0.3 years), 168 nonasthmatic children of smoking mothers (mean age ± SEM = 12.9 ± 0.2 years) had significantly lower mean percentage of predicted FEV_1 (mean ± SEM = 108.0 ± 1.4 vs. 101.4 ± 1.1, respectively, $p < 0.001$) and significantly lower FEF_{25-75} (103.0 ± 2.3 vs. 88.2 ± 1.5, respectively, $p < 0.001$). These effects were independent of personal smoking by the child.

Table 7-10. Recent epidemiologic studies on the effects of passive smoking on lung function in children

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
O'Connor et al. (1987)	97 children (12.8 ± 0.3 yr.) of smoking mothers; 168 children (12.9 ± 0.2 yr.) of nonsmoking mothers in Boston, Massachusetts	Parental questionnaire	Nonsmoking mothers vs. smoking mothers: FEV_1 (% predicted) 108.0 ± 1.4 vs. 101.4 ± 1.1 ($p<0.001$); FEF_{25-75} (% predicted) 103.0 ± 2.3 vs. 88.2 ± 1.5 ($p<0.001$)	Independent of personal smoking habits
Lebowitz et al. (1987)	353 subjects aged 5.5 to 25 yr. in Tucson, Arizona	Parental questionnaire	Smoking mothers vs. non-smoking mothers FVC (residuals) +3.3 vs. -1.4 ($p<0.001$)	Interaction between family history of respiratory illnesses and passive smoking for $V_{max}50\%$ residuals
Tsimoyianis et al. (1987)	132 athletes exposed to ETS; 61 athletes not exposed to ETS	Self-reported exposure to ETS	OR of having low FEF_{25-75} 4.7 (1.1-20.8)	
Kauffmann et al. (1989b)	1,160 French children	Parental questionnaire	Loss of 10 mL of FEV_1, ($p=0.05$); loss of 15 mL/sec of FEF_{25-75} ($p<0.01$)	Independent of sex, town of origin, age, height, weight, and family aggregation of lung function
Chan et al. (1989b)	130 children of low birthweight at age 7 yr. in England	Maternal reports of cigarette smoking	Mean $V_{max}75\%$ (% predicted) in exposed vs. nonexposed 80.7 vs. 91.4 ($p<0.01$)	Independent of sex, birthweight, neonatal respiratory illness, and treatment

(continued on the following page)

Table 7-10. (continued)

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
Dijkstra et al. (1990)	634 children aged 6 to 12 yr. in The Netherlands	Parental questionnaire	Decrease in: FEV_1 (-1.8% [-0.2 to -3.31]); $FEF_{25-75\%}$ (-5.21% [-1.4 to -8.8]); PF (-2.8% [0.6 to -4.8])	Independent of maternal smoking during pregnancy
Strachan et al. (1990)	757 children in Scotland	Salivary cotinine levels	Negative correlation with $FEF_{25-75\%}$ ($p<0.05$) and $V_{max}75\%$ ($p<0.05$)	Approx. 7% difference between maximal exposure and no exposure
Martinez et al. (1992)	774 children enrolled at age 0 to 5 in Tucson, Arizona, and followed for several years	Parental questionnaire	15% lower levels of % predicted $FEF_{25-75\%}$ among children of mothers who smoked and had a low level of education	

[1]95% confidence intervals in parentheses.

Lebowitz and coworkers (1987) reported on the results of a longitudinal study of pulmonary function development in Tucson, Arizona. The authors analyzed 1,511 observations over an average followup period of 8.8 years in 353 subjects aged 5.5 to 25 years. The last available lung function value (as residuals after regressing the data with different power functions of age and height) was used as outcome. Residuals for vital capacity were significantly higher among subjects aged 14 years or less at entry whose mothers smoked cigarettes (mean = +3.3 vs. -1.4 among nonexposed subjects, $p < 0.001$). Parental smoking had no direct effect on outcome FEV_1 or $V_{max}50\%$, but showed significant interactions with personal smoking and parental history of airway obstructive diseases in their effects on $V_{max}50\%$; subjects who had started smoking or whose parents had airway obstructive diseases and were exposed to ETS had the lowest $V_{max}50\%$ residuals at the end of followup.

In subsequent reports, Lebowitz and Holberg (1988) and Tager and coworkers (1987) reanalyzed two sets of longitudinal pulmonary function data: the one on which the preceding study from Tucson, Arizona, was based (Lebowitz et al., 1987) and data for children of similar age from East Boston, Massachusetts (Tager et al., 1983). The objective was to determine if the different answers with regard to the effect of maternal smoking (significant for the Boston study; no effect for the Tucson study) were due to the use of different statistical tools. Applying the same multivariable analysis of covariance for both data sets, Lebowitz and Holberg (1988) confirmed the positive effect of maternal smoking of $FEF_{25-75\%}$ with the data from Boston ($p < 0.05$) and the lack of a significant effect of maternal smoking on $V_{max}50\%$ with the data from Tucson, Arizona. A first-order autoregressive model applied by Tager and collaborators (1987) to both data sets showed effects of maternal smoking on FEV_1 with the Boston data but not with the Tucson data. The authors concluded that the most likely factor responsible for the disparate results was the exposure difference in the two populations.

Tsimoyianis and collaborators (1987) compared the prevalence of low levels of $FEF_{25-75\%}$ (< 70% of predicted) in athletes exposed and unexposed to ETS (for more information on this study see Section 7.5.1). Of 132 exposed athletes, 18 (13.6%) had low $FEF_{25-75\%}$ compared with 2 of 61 (3.3%) unexposed athletes (OR = 4.7; 95% C.I.= 1.1, 20.8).

Kauffmann and collaborators (1989b) assessed familial factors related to lung function in a cross-sectional study of 1,160 French children. Levels of lung function (FEV_1 and $FEF_{25-75\%}$) were significantly lower in children with mothers who smoked when compared to those whose mothers were nonsmokers. The authors reported a loss of 10 mL of FEV_1 ($p < 0.05$) and of 15 mL/s of $FEF_{25-75\%}$ ($p < 0.01$) for every gram of tobacco smoked per day by the mother. These associations were independent of sex, town of origin, age, height, weight, and intrafamilial aggregation of lung function. There was no effect of paternal smoking on lung function.

Chan and coworkers (1989b) performed lung function tests in a cohort of 130 children of low birthweight (under 2,000 grams) at 7 years. These authors had previously reported on the respiratory outcome of these same children (see Section 7.5.1). Children of low birthweight whose mothers smoked had significantly lower values of percentage of predicted $V_{max}75\%$ than did low-birthweight children whose mothers did not smoke (80.7% vs. 91.4%, $p < 0.01$). This association was independent of sex, birthweight, neonatal respiratory illness, and treatment. As 92%

and 79% of mothers who smoked when the child was 7 years old were smokers before and during their pregnancy, respectively, it was not possible to determine whether the effect of maternal smoking was fetal or postnatal.

The study by Dijkstra and collaborators (1990) has been described earlier (Section 7.5.1). The authors studied, together with respiratory symptoms, lung function and its relationship with indoor exposures to ETS and nitrogen dioxide in a population of 634 Dutch children 6 to 12 years of age. When compared with unexposed children, children exposed to ETS had significantly lower levels of FEV_1 (−1.8%; 95% C.I. = −0.2, −3.3), $FEF_{25-75\%}$ (−5.2%; 95% C.I. = −1.4, −8.8) and Peak Flow (−2.8%; 95% C.I. = −0.6, −4.8). Adjustment for smoking by the mother when she was pregnant with the investigated child removed little of the effect of current ETS exposure on lung function. The authors suggested that this indicated that the associations seen at ages 6 to 12 years were not just mirroring harm that was caused when the children were exposed in utero to tobacco smoke components inhaled by the mother. There was no association between exposure to NO_2 and lung function.

A previously mentioned study by Strachan and coworkers (1990) (Section 7.5.1) included lung function measurements in 757 children. Lung function variables were adjusted for sex, height, and housing characteristics. The authors found a significant negative correlation between salivary cotinine concentrations and levels of $FEF_{25-75\%}$ ($p < 0.05$) and $V_{max}75\%$ ($p < 0.05$). For these indices, the difference between adjusted mean values for the top and bottom quintiles of salivary cotinine was of the order of 7% of the mean value in the children with undetectable levels.

The longitudinal study by Martinez and coworkers (1992) has been reviewed earlier (Section 7.6.1). In addition to their findings on incidence of childhood asthma, these authors reported that, at the end of followup, children of mothers with 12 or fewer years of formal education and who smoked 10 or more cigarettes per day had 15% lower mean values for percentage of predicted $FEF_{25-75\%}$ than did children of mothers of the same level of education who were nonsmokers or smoked fewer than 10 cigarettes per day. Maternal smoking had no effect on percentage of predicted $FEF_{25-75\%}$ values in children of mothers who had at least some education beyond high school. Female children of smoking mothers ($\geq$ 10 cig./day) had 7% higher vital capacity than did female children of mothers who were nonsmokers or light smokers (< 10 cig./day), and this was independent of maternal education. All differences were still significant after controlling for parental history of respiratory disease.

7.8.2. Summary and Discussion on Pulmonary Function in Children

This report concludes that there is a causal relationship between ETS exposure and reductions in airflow parameters of lung function (FEV_1, $FEF_{25-75\%}$, $V_{max}50\%$, or $V_{max}75\%$) in children. For the population as a whole, these reductions are small relative to the intraindividual variability of each lung function parameter; for $FEF_{25-75\%}$, for example, reductions range from 3% to 7% of the levels seen in unexposed children, depending on the study analyzed. Groups of particularly susceptible or heavily exposed subjects have larger decrements: Exposed children of low birthweight, for example, had 12% lower $V_{max}75\%$ than did children of similar birthweight who were not exposed to ETS (Chen, 1989). Likewise, children of less educated mothers who smoked 10 or more cigarettes per day were shown to have 15% lower mean $FEF_{25-75\%}$ than children of less educated mothers who did not smoke or smoked fewer

than 10 cigarettes per day. This stronger effect may be explained by Strachan and coworkers' (1989) finding that children of lower socioeconomic status have higher salivary cotinine levels, for any amount of parental smoking, than do children of higher socioeconomic status.

The studies reviewed suggest that a continuum of exposures to tobacco products starting in fetal life may contribute to the decrements in lung function found in older children. In fact, exposure to tobacco smoke products inhaled by the mother during pregnancy may contribute significantly to these changes, but there is strong evidence indicating that postnatal exposure to ETS is an important part of the causal pathway.

New longitudinal studies have demonstrated that young adults who were exposed earlier in life to ETS are also more susceptible to the effects of active smoking (Lebowitz et al., 1987). In addition, Sherrill and collaborators (1990) showed, in a longitudinal study, that children who entered a longitudinal study with lower levels of lung function still had significantly lower levels later in life. The high degree of tracking shown by these spirometric parameters implies that the decrements in lung function related to passive smoking may persist into adulthood. Although the subsequent rates of decline in lung function of these subjects have yet to be studied in detail, the findings by Sherrill and coworkers (1990) support the idea proposed by the Surgeon General's report (U.S. DHHS, 1986) that, by the mechanisms described above, passive smoking may increase the risk of chronic airflow limitation.

7.9. PASSIVE SMOKING AND RESPIRATORY SYMPTOMS AND LUNG FUNCTION IN ADULTS

Both the NRC report (1986) and the Surgeon General's report (U.S. DHHS, 1986) extensively reviewed the evidence then available on involuntary smoking and respiratory health in adults. The Surgeon General's report concluded that healthy adults exposed to ETS may have small changes on pulmonary function testing but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to ETS alone. The report added that the small magnitude of the effect implied that a previously healthy individual would not develop chronic lung disease solely on the basis of ETS exposure in adult life. It was suggested that small changes in lung function may be markers of an irritant response, possibly transient, to the irritants known to be present in ETS.

The NRC report concluded that it was difficult to document the extent to which a single type of exposure like ETS affects lung function. The report attributed this difficulty to the large number of factors, including other exposures, that affect lung function over a lifetime. The report added that results in adults should be evaluated for possible misclassification of ex-smokers or occasional smokers as nonsmokers, as well as possible confounding by occupational exposures to other pollutants. The authors of the report considered it "unlikely that exposure to ETS can cause much emphysema" (page 212), but that, "as one of many pulmonary insults, ETS may add to the total burden of environmental factors that become sufficient to cause chronic airway or parenchymal disease" (page 212).

7.9.1. Recent Studies on Passive Smoking and Adult Respiratory Symptoms and Lung Function

Six recent studies of respiratory symptoms and lung function in adults are presented in Table 7-11.

Svendsen and collaborators (1987) studied longitudinal data from 1,245 married American men aged 35 to 57 years who reported that they had never smoked. Subjects who had smoking wives had significantly higher mean levels of exhaled carbon monoxide (7.7 vs. 7.1 ppm, $p < 0.001$) but not of serum thiocyanate. These men also had lower levels of age- and height-adjusted FEV_1 (mean difference = 99 mL; 95% C.I. = 5, 192.4 mL). However, those with wives who smoked 20 or more cigarettes per day had higher mean adjusted FEV_1 (3,549 mL) than those with wives who smoked 1 to 19 cigarettes per day (3,412 mL), whereas nonexposed subjects had mean adjusted FEV_1 of 3,592 mL.

Kalandidi and coworkers (1987) studied 103 Greek ever-married women aged 40 to 79 who were admitted in 1982 and 1983 to a hospital in Athens with obstructive or mixed type reduction of pulmonary function, without improvement after bronchodilatation. The women

Table 7-11. Recent epidemiologic studies on the effects of passive smoking on adult respiratory symptoms and lung function

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Svendsen et al. (1987)	1,245 married American nonsmoking men aged 35 to 57 yr.	Subject's report of spouse's smoking habits	FEV_1	Mean difference of 99 mL (5-192 mL)	No dose-response effect
Kalandidi et al. (1987)	103 Greek women with obstructive lung disease aged 40 to 79 yr.; 179 control women; all nonsmokers	Subject's report of spouse's smoking habits	See population studied	OR = 1.9 (1.0, 4.0)	No dose-response effect
Masi et al. (1988)	636 subjects aged 15 to 36 yr.	Subject's report of exposure to ETS	Maximal expiratory flows (MEF); diffusing capacity (DC)	Inverse relationship with ETS exposure at home in men for MEF; with exposure at work in women for DC	Strongest effect in men for exposure before age 17 yr.
Kauffmann et al. (1989a)	2,220 American women aged 25 to 69 yr.; 3,850 French women aged 25 to 59 yr.	Subject's report of spouse's smoking habits	Self-report of respiratory symptoms; lung function	OR = 1.3 for wheezed in U.S. sample; OR = 1.4 for cough and OR = 1.2 for dyspnea in French sample; lower FVC and FEV_1 ($p=0.01$) in French women age $\geq$40 yr.	Increased risks for respiratory symptoms did not reach statistical significance

(continued on the following page)

Table 7-11. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Hole et al. (1989)	7,997 subjects aged 45 to 64 yr. in Scotland	Questionnaires answered by household members	Cardiorespiratory symptoms; lung function	No significant increase in risk of symptoms; decrease in FEV_1 (60 mL) when a cohabitee smoked >15 cig./day	
Schwartz and Zeger (1990)	100 student nurses in Los Angeles, California	Questionnaire answered by subject on presence of a smoking roommate	Respiratory symptoms assessed by self-administered questionnaire	Increased risk of having phlegm (OR = 1.4 [1.1, 1.9])	Over-reporting by exposed subjects may bias results

[1]95% confidence intervals in parentheses.

denied that they had ever been smokers, and their husbands' smoking habits were compared with those of 179 ever-married controls of the same age selected from visitors to the hospital. Patients were 1.9 times more likely to have smoking spouses than were controls (95% C.I. = 1.0, 4.0). However, odds ratios were higher for women whose spouses smoked 20 or fewer cigarettes per day (2.5) than for those whose spouses smoked more than 20 cigarettes per day. The unusually high number of nonsmoking women hospitalized with chronic lung disease in a 2-year period suggests that some could have severe asthma unresponsive to bronchodilators and that the results could in part illustrate exacerbation of symptoms in asthmatic women exposed to ETS.

Masi and coworkers (1988) mailed questionnaires to 818 subjects aged 15 to 35 who had previously performed detailed lung function testing and carboxyhemoglobin (COHb) measurements. A total of 636 subjects responded to the questionnaire, and 293 denied having smoked regularly before the date of the lung function tests. All but five subjects had COHb values below 5 grams %. Questionnaires assessed past and present ETS exposure, both at home and at work. Indices of cumulative exposure to ETS at home and at work were calculated from the number of reported smokers on each location, the smoking conditions reported for each area, and the number of years of exposure. In men, there were significant inverse relationships between cumulative exposure to ETS in the home and maximal expiratory flows at low lung volumes. A more detailed analysis showed that in these subjects, exposure before 17 years of age had the strongest effects on lung function, whereas exposure in the 5 years preceding the lung function tests had no effect on lung function. Exposure at work significantly decreased the diffusing characteristics of the lung in women.

Kauffmann and collaborators (1989a) compared the results obtained from a parallel analysis of the association of passive smoking with respiratory symptoms and lung function in 2,220 American women aged 25 to 69 years and 3,855 French women aged 25 to 59 years. Women were classified according to their personal and current spouse's smoking habits. After adjusting for age, city of origin, educational level, and occupational exposure, ever-passive-smokers (excluding active smokers) had significantly more wheeze than true never-smokers (i.e., never active and with nonsmoking spouse) in the U.S. sample (OR of approximately 1.3; C.I. cannot be calculated). There was a positive trend for French passive smokers to have more chronic cough (OR = 1.4) and dyspnea (OR = 1.2), but both results could be due to chance (95% C.I. = 0.8, 2.4 and 0.9, 1.6, respectively). In both samples, no significant decrease of lung function was observed for passive smokers compared with true never-smokers in the whole sample, although FEV_1/FVC values for ever-passive-smokers tended to be intermediate between those of true never-smokers and ex-smokers or active smokers. French women aged 40 or older who were passive smokers had significantly lower FVC ($p < 0.01$) and FEV_1 ($p < 0.01$) than did true never-smokers, but no such effect was seen among American women of the same age.

Hole and coworkers (1989) studied cardiorespiratory symptoms and mortality in a cohort of 7,997 subjects aged 45 to 64 and followed for 11 years in urban west Scotland. A self- administered questionnaire was used in 1972-76 to assess respiratory symptoms and active smoking by each member of the household. When compared with true never-smokers (i.e., persons who were not active smokers and did not live with an active smoker), passive

smokers were invariably at a higher risk of having each cardiorespiratory symptom examined (including infected sputum, persistent sputum, and dyspnea), but all 95% confidence intervals for odds ratios included 1. FEV_1 (adjusted for sex, age, and height) was significantly higher in true never-smokers than in passive smokers ($p < 0.01$), but this effect was mainly due to the low adjusted FEV_1 of passive smokers with high exposure (i.e., exposed to a cohabitee who smoked > 15 cig./day; mean = 1.83 L) when compared with those with low exposure (mean = 1.89 L) or with no exposure (mean = 1.88 L). This study was initiated when there was little concern for the possible ill effects of passive smoking and is based on self-reports of active smoking by cohabitees. It is thus probably not affected by classification bias due to overreporting of symptoms by smokers.

Schwartz and Zeger (1990) studied data from a cohort of approximately 100 student nurses in Los Angeles who kept diaries of acute respiratory symptoms (cough, phlegm, and chest discomfort) and for whom data on exposure to passive smoking and air pollution were available. After controlling for personal smoking, a smoking roommate increased the risk of an episode of phlegm (OR = 1.4; 95% C.I. = 1.1, 1.9) but not of cough. The authors also excluded asthmatics (on the assumption that medication could bias the results) and found that in this case, the odds ratio of having phlegm increased to 1.8 (95% C.I. = 1.3, 2.3). The greater sensitivity of diaries of acute symptoms such as those used herein, compared with the indices of period prevalence of symptoms used in other studies, may have increased the power of this study. However, overreporting by exposed subjects is still a possible source of bias in a study that is solely based on self-report of symptoms.

7.9.2. Summary and Discussion on Respiratory Symptoms and Lung Function in Adults

Recent studies have confirmed the conclusion by the Surgeon General's report (U.S. DHHS, 1986) that adult nonsmokers exposed to ETS may have small reductions in lung function (approximately 2.5% lower mean FEV_1 in the studies by Svendsen et al. [1987] and Hole et al. [1989]). Using modern statistical tools designed for longitudinal studies, new evidence also has emerged suggesting that exposure to ETS may increase the frequency of respiratory symptoms in adults. These latter effects are estimated to be 30% to 60% higher in ETS-exposed nonsmokers compared to unexposed nonsmokers.

Because active smoking causes significant reductions in lung function and significant increases in prevalence of respiratory symptoms (U.S. DHHS, 1984), the reported effects of passive smoking in adults are biologically plausible. From a quantitative point of view, effects of passive smoking on lung function are approximately comparable to those reported for light (< 10 cig./day), male active smokers (Camilli et al., 1987). However, because of the self-selection of smokers and other factors, it is difficult to make direct quantitative comparisons between the effects of active and passive smoking. The process of self-selection is likely to occur among smokers by which more susceptible individuals never start smoking or quit smoking early in life (the "healthy smoker" effect). Therefore, lower lifetime doses may be required to elicit effects among nonsmokers than among smokers. The different nature of ETS and MS also has been discussed in previous chapters and must be taken into account when comparing effects of active and passive smoking.

Several sources of bias and confounding factors need to be considered in studies of the effects of single exposures in adults. Classification bias due to underreporting of active smoking or past smoking may significantly affect the results of these studies. Because there is marital aggregation of smoking (i.e., smokers tend to marry smokers, and nonsmokers are more prone to marry nonsmokers), this source of misclassification is more probable among spouses of smokers and may introduce differential biases in some studies. The resulting small overestimation of effect may be nevertheless substantial for effects that are particularly subtle, such as those described for ETS exposure in adults. In addition, recent public concern with passive smoking may increase the awareness of respiratory symptoms in exposed subjects, who may be thus more prone to report symptoms than are unexposed subjects. Studies using objective measures of lung function obviously are not affected by the latter type of bias.

Adults are exposed to multiple sources of potentially harmful substances during their lifetimes, and it is not always possible to control for the effects of these substances because they often are unknown or unmeasurable. In general, the majority of these exposures should introduce nondifferential error to the studies, which would lead to underestimates of the true effects. For example, a significant nondifferential error may be introduced by ETS exposure during childhood, which is known to cause decrements in lung function (see Section 7.7) that may be carried into adulthood. ETS exposure during childhood also is known to cause childhood respiratory diseases (see Sections 7.3, 7.5, and 7.6). Such childhood respiratory diseases, whatever the cause, also may be reflected in decreased respiratory health in adulthood. These effects have not been accounted for in the studies of ETS exposure and lung function in adults, but it is likely that they would lead to underestimates of the ETS effects in the adult studies.

Conversely, effects of ETS would be overestimated if a certain noxious exposure were more likely to occur among ETS-exposed subjects. In this sense, social factors need to be accurately controlled, because prevalence of smoking is significantly higher among less educated than among higher educated subjects (Pierce et al., 1989). Most reviewed studies have controlled for indices of socioeconomic level in a satisfactory manner. Finally, lifestyles may differ between spouses of smokers and those of nonsmokers, but it is not possible to determine a priori the effect of this confounder on the relationship between passive smoking and respiratory health.

The influence of these factors and sources of bias, together with the subtlety of the effects, may explain the inconsistent and sometimes contradictory results of the studies reviewed in this report. In fact, such variability should be expected, particularly for studies with relatively low power (i.e., low probability of finding a statistically significant difference when a difference really exists). The lack of a dose-response relationship in some studies also may be explained by the multiplicity of uncontrolled factors that may affect lung function.

In summary, recent evidence suggests that passive smoking has subtle but statistically significant effects on the respiratory health of nonsmoking adults.